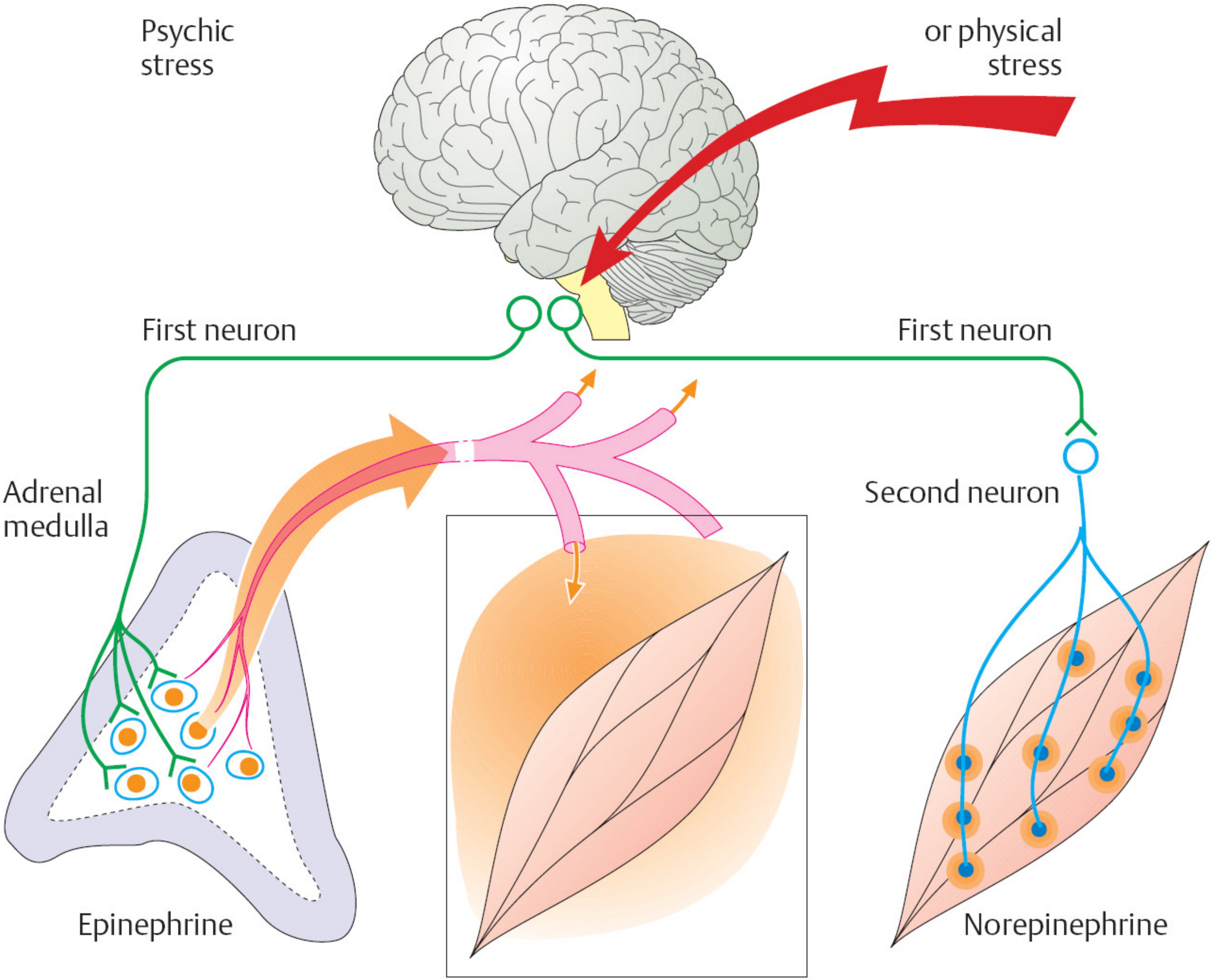
Chapter 9

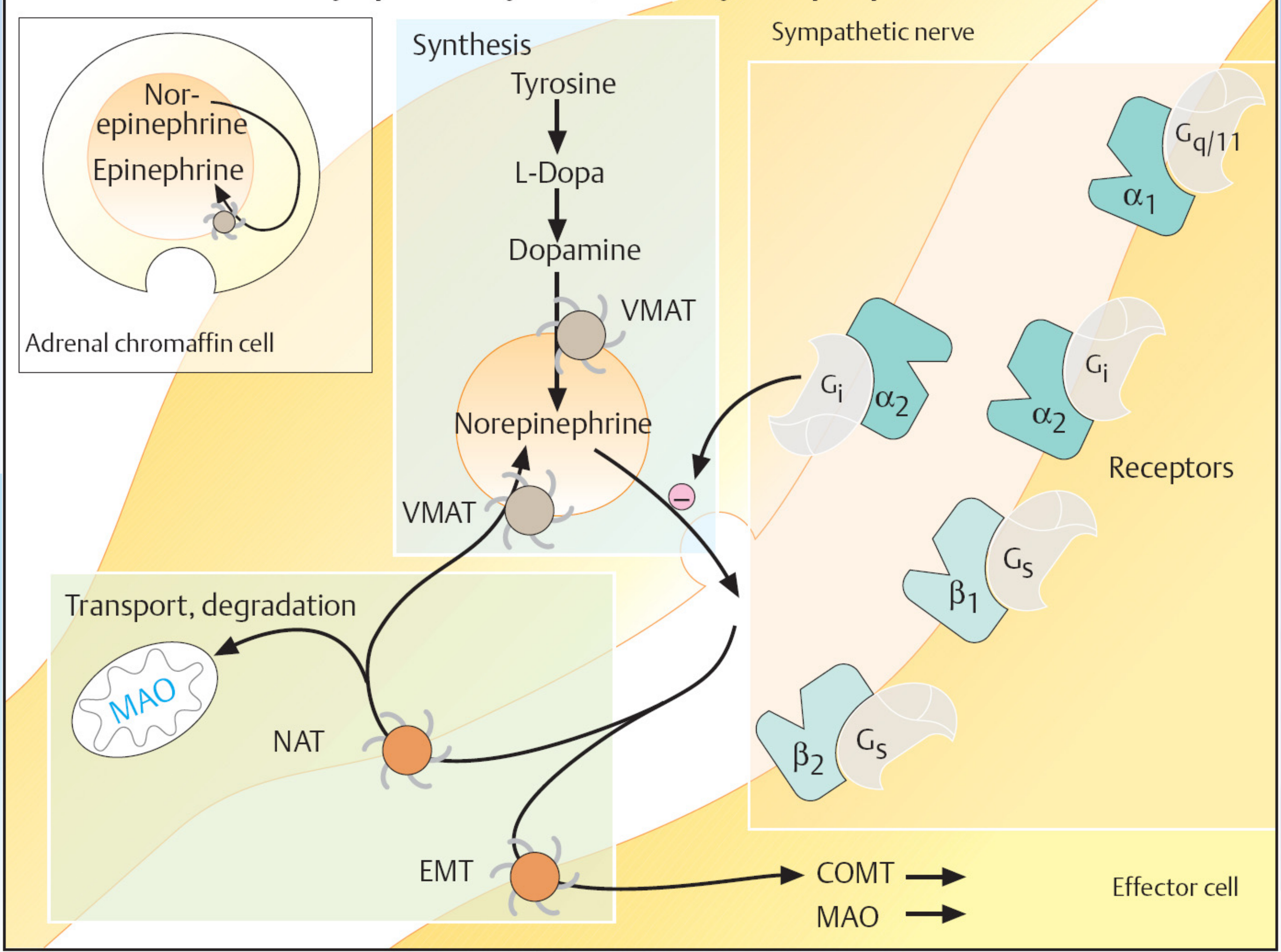
Adrenoceptor Agonists & Sympathomimetic Drugs

References
Basic & Clinical Pharmacology - 11th Ed
Katzung & Trevor's Pharmacology Examination and Board Review, Ninth Edition
Lippincott's Illustrated Reviews Pharmacology, 4th Edition
Color Atlas of Pharmacology 3rd Ed

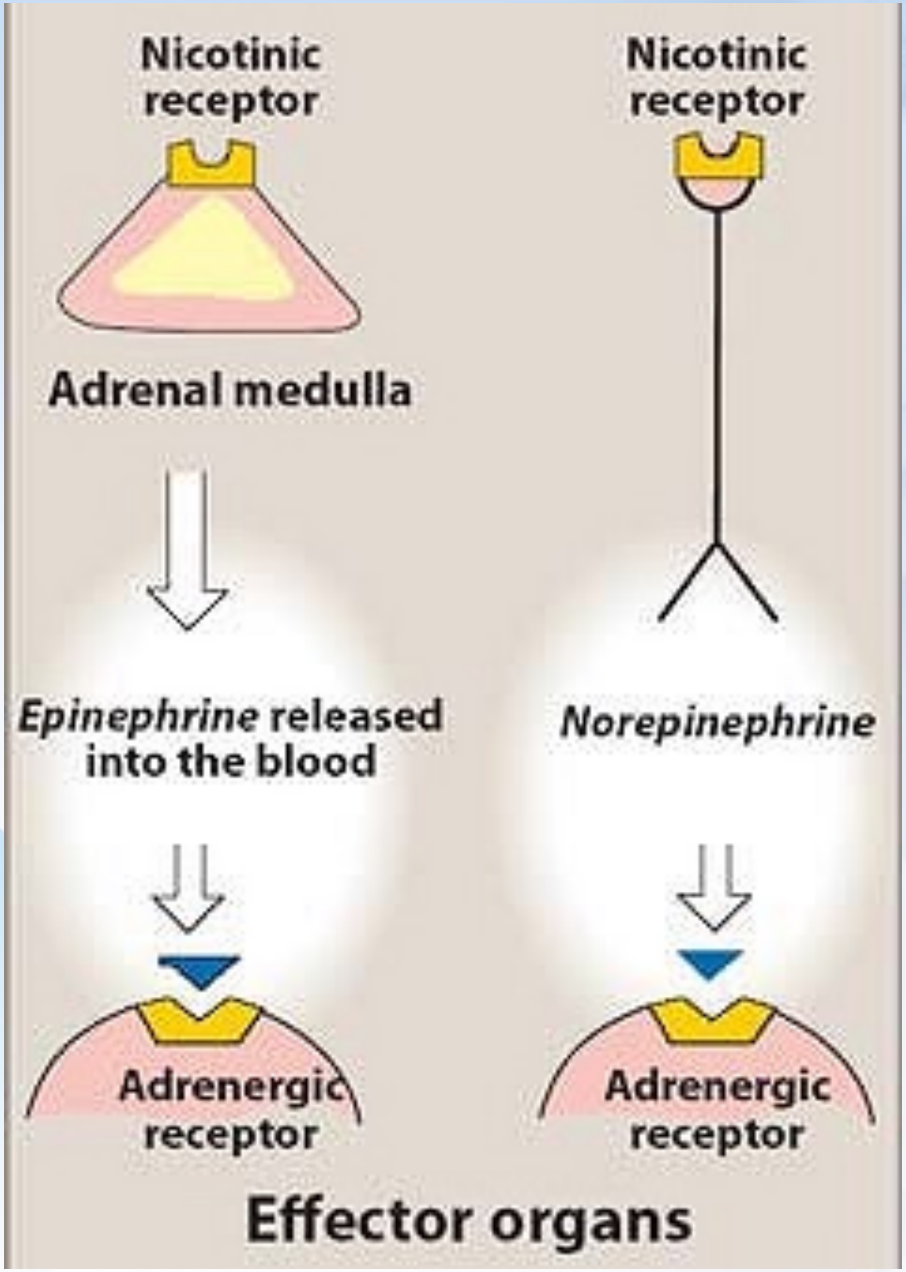
Epinephrine as hormone, norepinephrine as transmitter

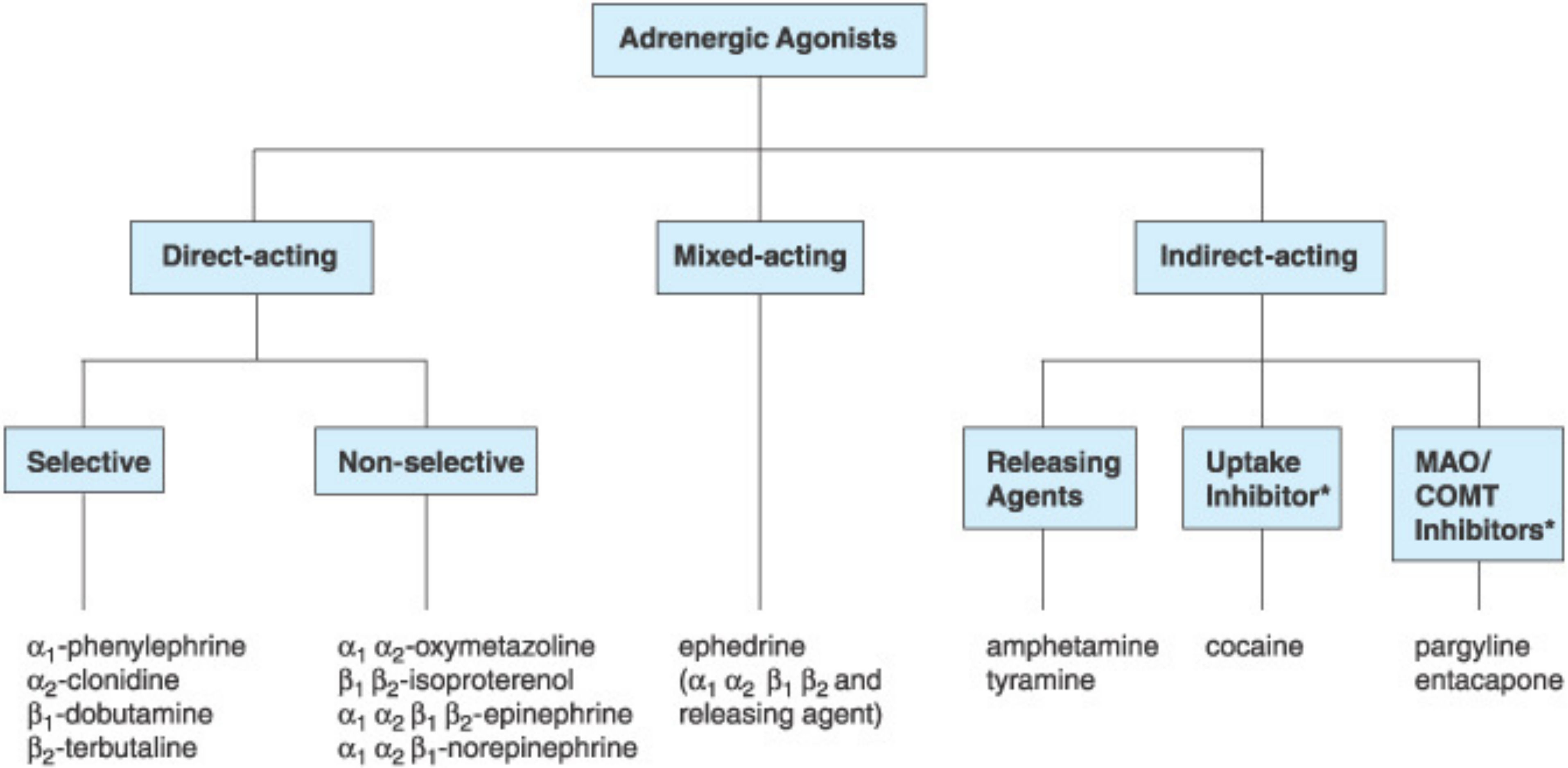


Second neuron of sympathetic system, varicosity, norepinephrine release



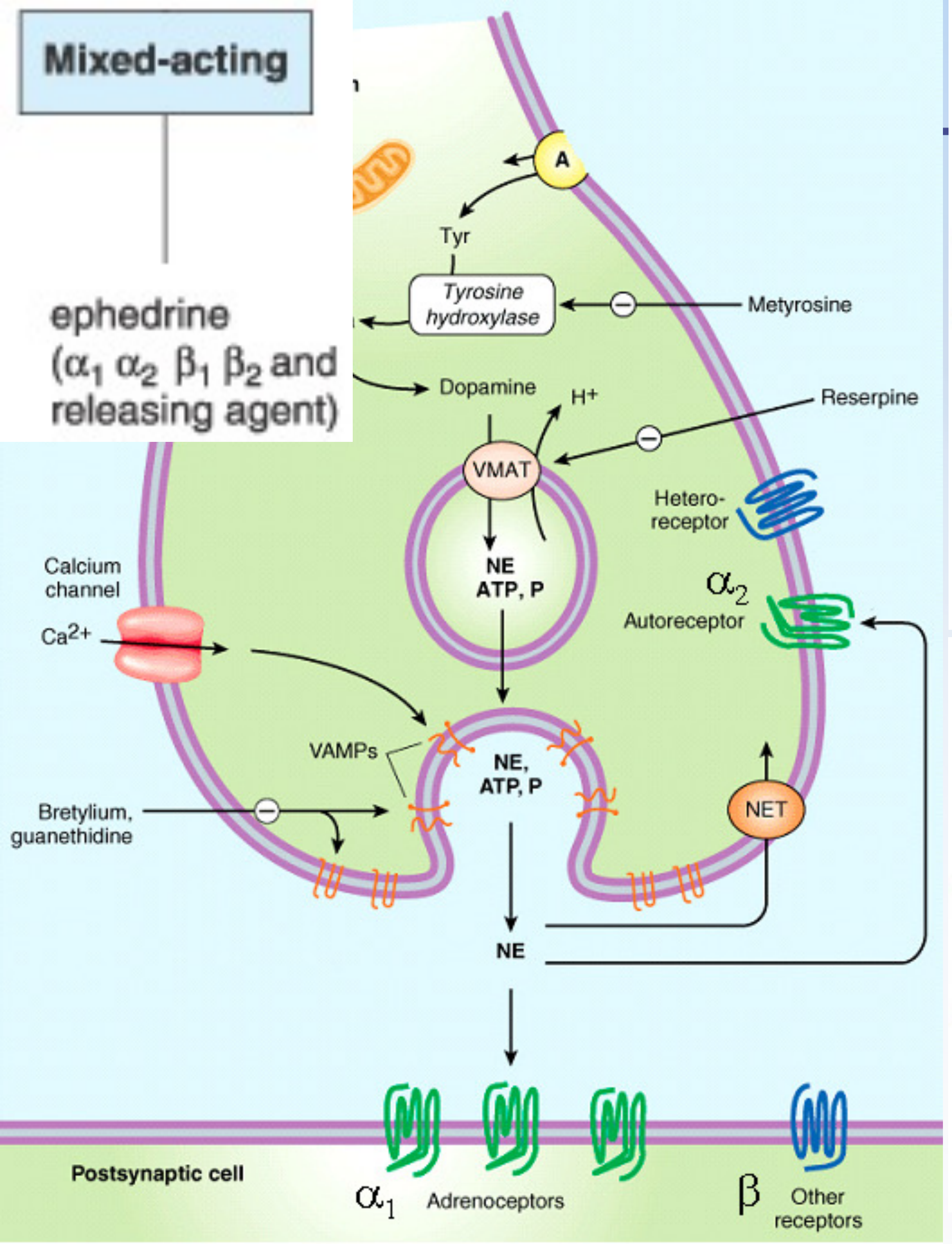
Adrenoceptor Agonists & Sympathomimetic Drugs: Introduction




Adrenergic Agonists
Direct-acting
Mixed-acting
Indirect-acting
Selective
Non-selective
Releasing Agents
Uptake Inhibitor*
MAO/ COMT Inhibitors*
α_1-phenylephrine
α_2-clonidine
β_1-dobutamine
β_2-terbutaline
α_1 α_2-oxymetazoline
β_1 β_2-isoproterenol
α_1 α_2 β_1 β_2-epinephrine
α_1 α_2 β_1-norepinephrine
ephedrine
(α_1 α_2 β_1 β_2 and releasing agent)
amphetamine
tyramine
cocaine
pargyline
entacapone

Mixed-acting

- ephedrine (α_1 α_2 β_1 β_2 and releasing agent)



Direct-acting

- **Selective**
  - α_1-phenylephrine
  - α_2-clonidine
  - β_1-dobutamine
  - β_2-terbutaline
- **Non-selective**
  - α_1 α_2-oxymetazoline
  - β_1 β_2-isoproterenol
  - α_1 α_2 β_1 β_2-epinephrine
  - α_1 α_2 β_1-norepinephrine

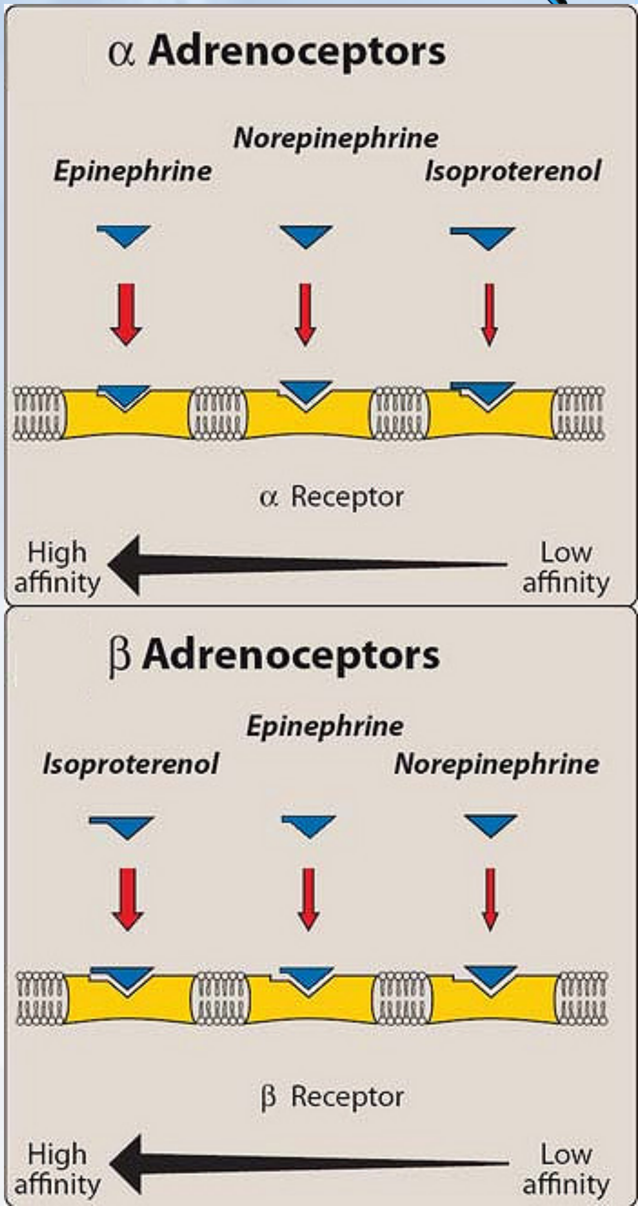
Indirect-acting

- **Releasing Agents**
  - amphetamine
  - tyramine
- **Uptake Inhibitor***
  - cocaine
- **MAO/ COMT Inhibitors***
  - pargyline
  - entacapone

Type	Actions	Effects
α_1	Contraction Contraction (dilates pupil) Erects hair Contraction Increases force of contraction	↑ IP_3, DAG common to all
α_2	Probably multiple Aggregation Inhibition of transmitter release Contraction Inhibition of lipolysis	↓ cAMP common to all
β_1	Increases force and rate of contraction Increases renin release	↑ cAMP common to all
β_2	Promotes smooth muscle relaxation Promotes potassium uptake Activates glycogenolysis	
β_3	Activates lipolysis Dilates renal blood vessels Modulates transmitter release	

Molecular Pharmacology Underlying the Actions of Sympathomimetic Drugs

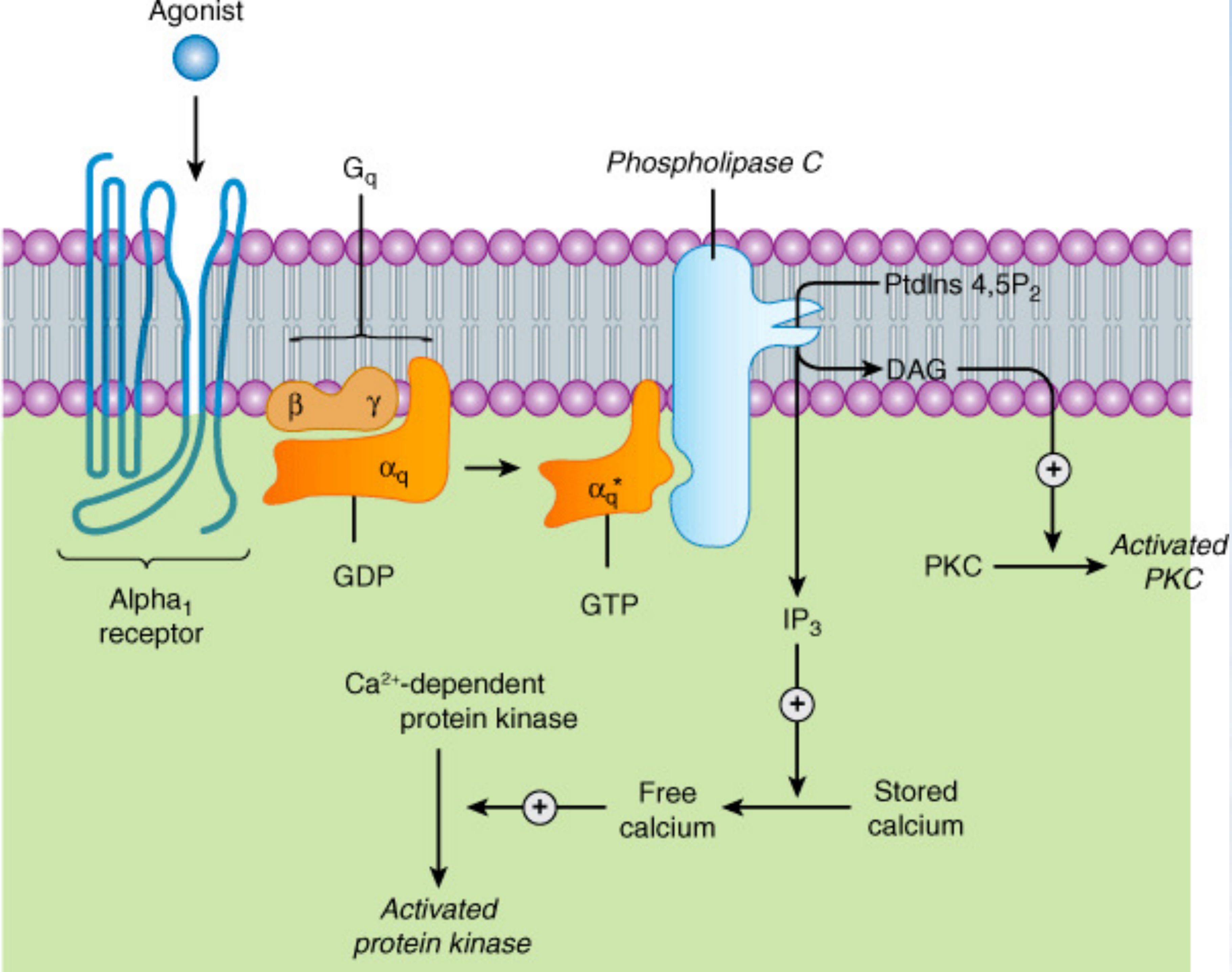
- Adrenoreceptors were initially characterized pharmacologically, with receptors having the comparative potencies
  - epinephrine ≥ norepinephrine >> isoproterenol
  - isoproterenol > epinephrine ≥ norepinephrine.

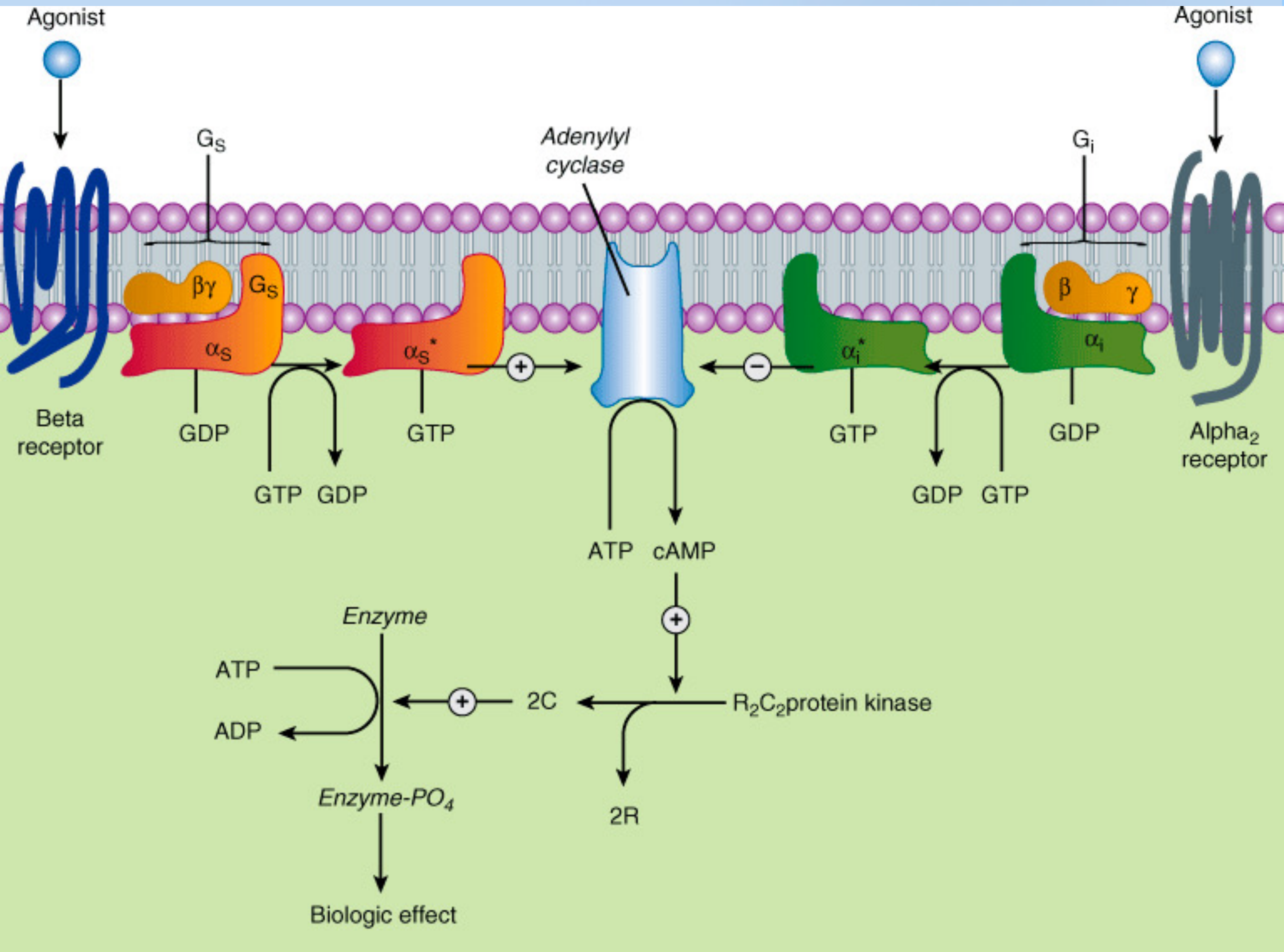


Receptor Types (α, β, Dopamine)

- Alpha Receptors
- Beta Receptors

Type	Actions	Effects
α_1	vascular smooth muscle→Contraction (dilates pupil Erects hair Prostate→Contraction Increases force of contraction	Agonist: phenylephrine antagonist: prazosin ↑ IP_3, DAG common to all
α_2	Probably multiple Platelets→Aggregation Inhibition of transmitter release	Agonist: clonidine antagonist: yohimbine ↓ cAMP common to all
β	Increases force and rate of contraction increases renin release Promotes smooth muscle relaxation Promotes potassium uptake Activates glycogenolysis Activates lipolysis Dilates renal blood vessels Modulates transmitter release	Agonist: isoproterenol antagonist: propranolol ↑ cAMP common to all


Agonist
G_q
Phospholipase C
PtdIns $4,5P_2$
DAG
β
γ
α_q
α_q^*
+
PKC
Activated PKC
GDP
GTP
Alpha$_1$ receptor
IP_3
+
Ca^{2+}-dependent protein kinase
Free calcium
Stored calcium
+
Activated protein kinase


Agonist
Agonist
Gs
Adenylyl cyclase
Gi
βγ
Gs
β
γ
αs
αs*
αi*
αi
Beta receptor
GDP
GTP
GTP
GDP
Alpha2 receptor
GTP GDP
GDP GTP
ATP cAMP
Enzyme
ATP
ADP
2C
R2C2protein kinase
Enzyme-PO4
2R
Biologic effect

- Dopamine Receptors
  - D1 receptor → stimulate→adenylyl cyclase activity
    - cAMP ↑
    - vasodilator.
  - D2 receptors → inhibit→adenylyl cyclase activity
    - cAMP ↓
    - calcium influx ↓

Type	Actions	Effects
D_1	smooth muscle relaxation	↑ cAMP
D_2	Dilates renal blood vessels Modulates transmitter release	↓ cAMP

Receptor Selectivity

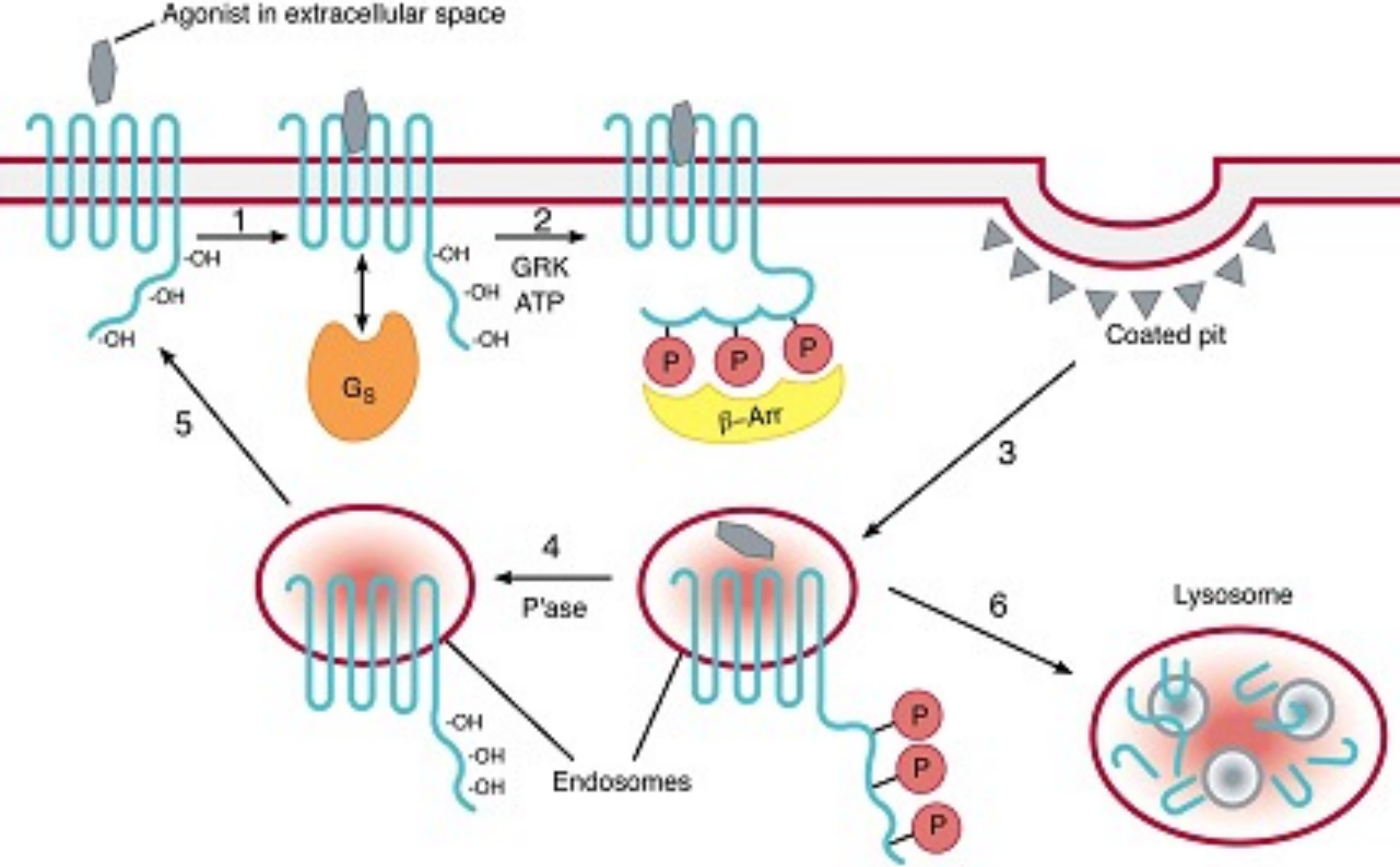
	Relative Receptor Affinities
Alpha agonists:	
Phenylephrine, methoxamine	$\alpha_1 > \alpha_2 >>>>> \beta$
Clonidine, methylnorepinephrine	$\alpha_2 > \alpha_1 >>>>> \beta$
Mixed alpha and beta agonists :	
Norepinephrine	$\alpha_1 = \alpha_2; \beta_1 >> \beta_2$
Epinephrine	$\alpha_1 = \alpha_2; \beta_1 = \beta_2$
Beta agonists :	
Dobutamine	$\beta_1 > \beta_2 >>>> \alpha$
Isoproterenol	$\beta_1 = \beta_2 >>>> \alpha$
Albuterol, terbutaline, metaproterenol, ritodrine	$\beta_2 >> \beta_1 >>>> \alpha$
Dopamine agonists :	
Dopamine	$D_1 = D_2 >> \beta >> \alpha$
Fenoldopam	$D_1 >> D_2$

Receptor Regulation

Adrenoceptor Polymorphisms

The Norepinephrine Transporter

Receptor Regulation

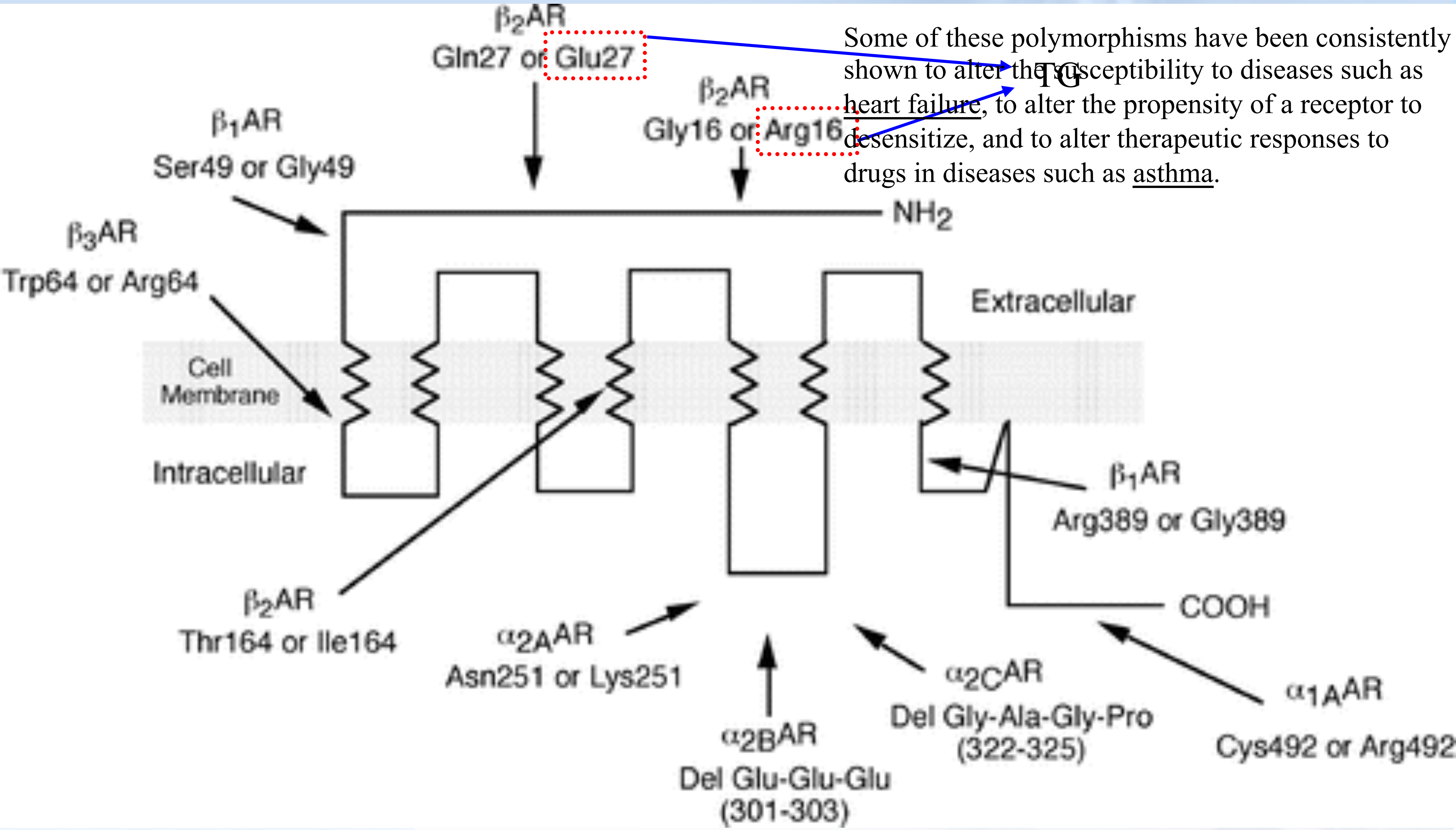


Adrenoceptor Polymorphisms

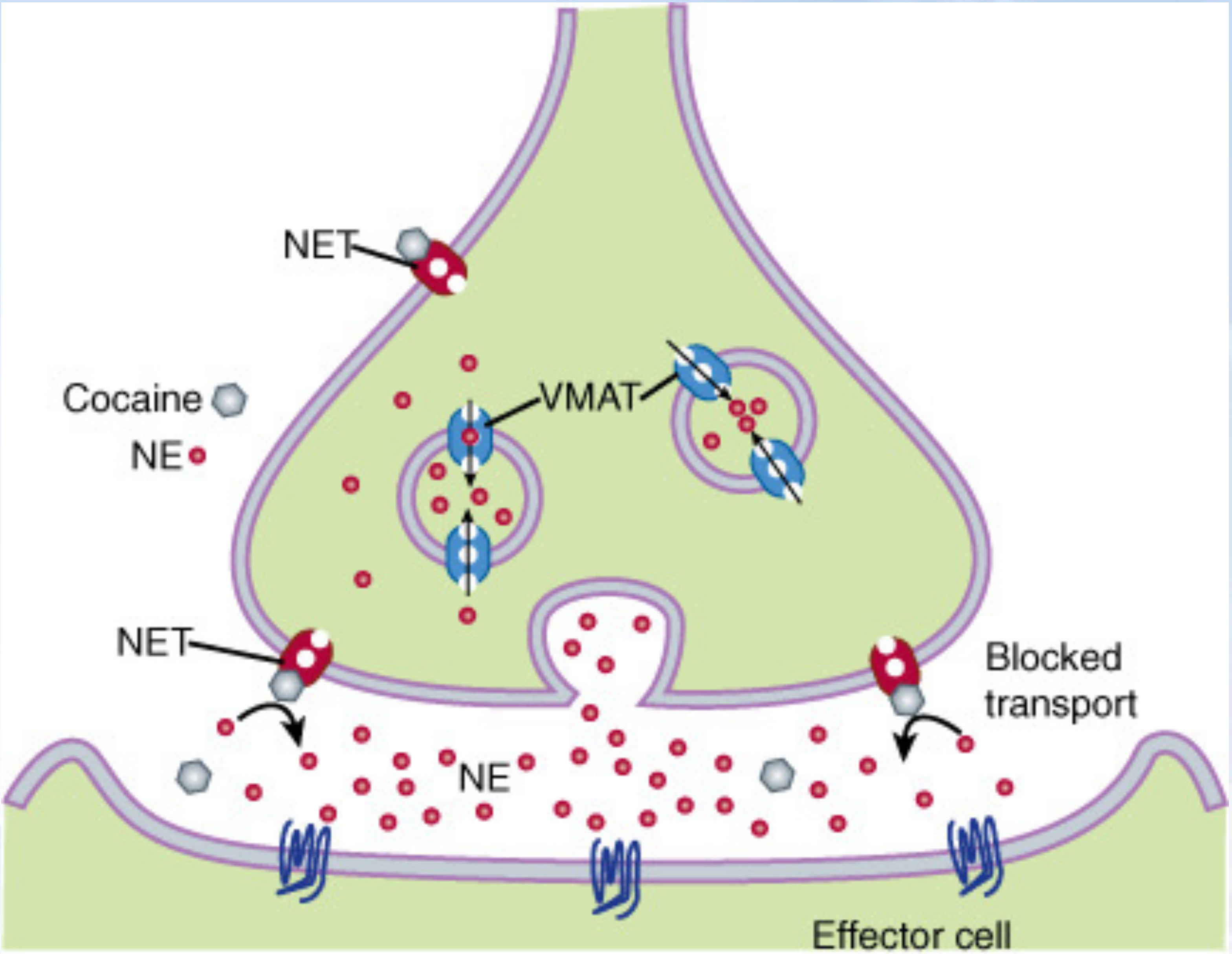
~haplotype~

Some of these polymorphisms have been consistently shown to alter the susceptibility to diseases such as heart failure, to alter the propensity of a receptor to desensitize, and to alter therapeutic responses to drugs in diseases such as asthma.

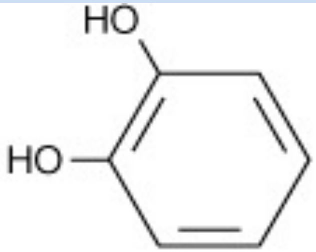
TG



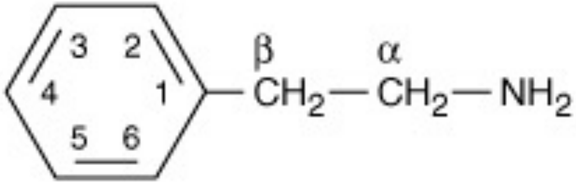
The Norepinephrine Transporter



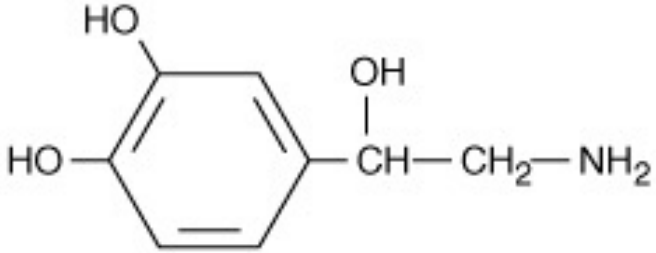
Medicinal Chemistry of Sympathomimetic Drugs



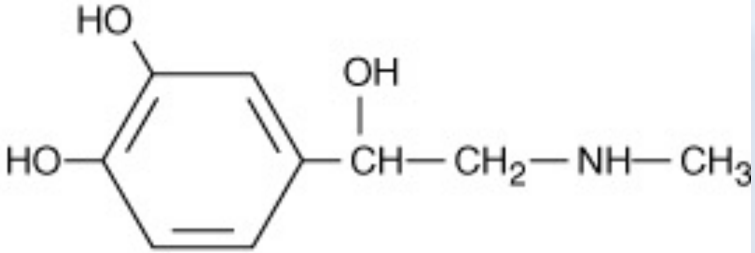
Catechol



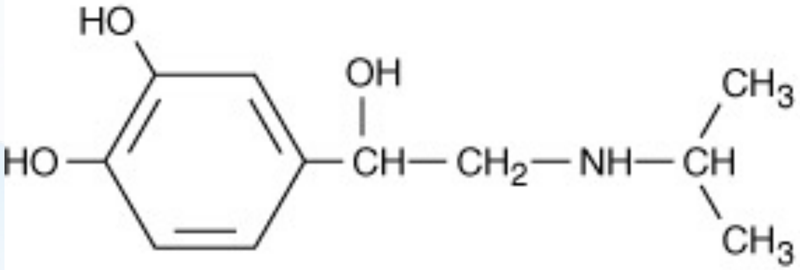
Phenylethylamine



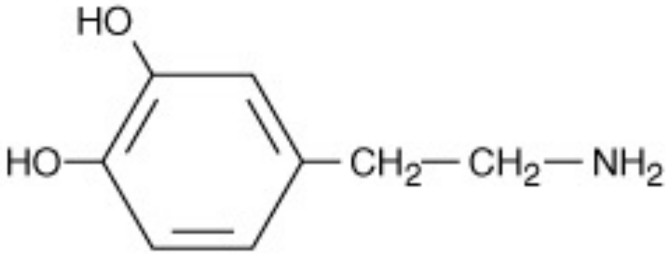
Norepinephrine



Epinephrine



Isoproterenol



Dopamine

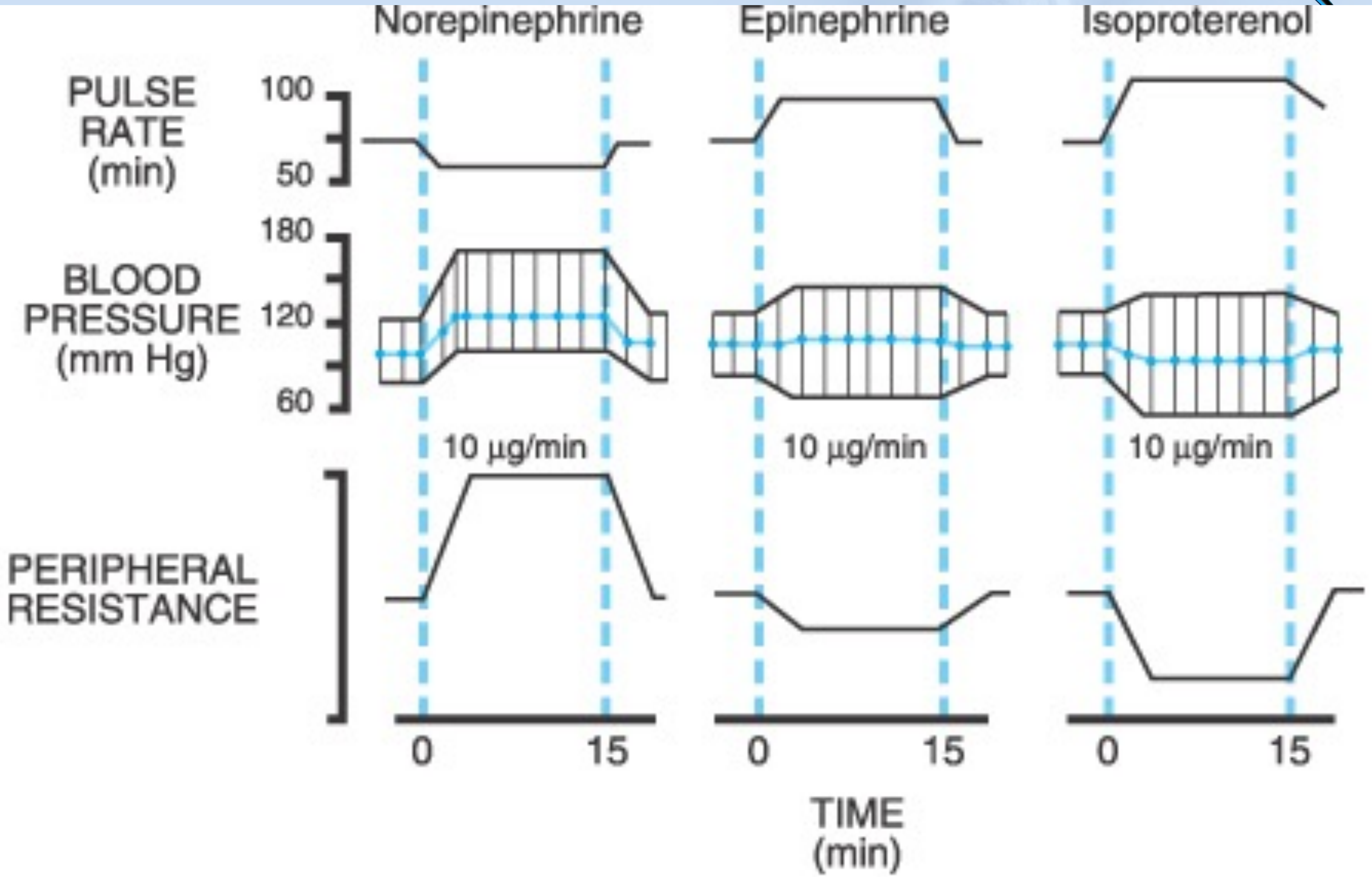
Organ System Effects of Sympathomimetic Drugs

- Cardiovascular System
  - Effects of $Alpha_1$-Receptor Activation
  - Effects of $Alpha_2$-Receptor Activation
  - Effects of Beta-Receptor Activation
  - Effects of Dopamine-Receptor Activation
- Noncardiac Effects of Sympathomimetics

Type	Actions	Drugs	Drugs
α_1	vascular smooth muscle→Contraction dilates pupil Prostate→Contraction	Midodrine, phenylephrine Naphazoline, oxymetazoline, methoxamine	Norepinephrine Epinephrine (oxymetazoline)
α_2	Platelets→Aggregation Inhibition of transmitter release	Clonidine, moxonidine methylnorepinephrine	
β_1	Increases force and rate of contraction increases renin release	Dobutamine,dopamine	Epinephrine <u>Isoproterenol</u>
β_2	Respiratory→smooth muscle relaxation Liver→Activates glycogenolysis	Albuterol, terbutaline, metaproterenol, ritodrine	
β_3	Fat cells →Activates lipolysis		
D_1	smooth muscle relaxation	Fenoldopam, Dopamine	
D_2	Dilates renal blood vessels Modulates transmitter release	Bromocriptine	

Cardiovascular Responses to Sympathomimetic Amines.

	Phenylephrine ($\alpha_1 > \alpha_2$)	Epinephrine ($\alpha_1, \alpha_2, \beta_1, \beta_2$)	Isoproterenol (β_1, β_2)
Vascular resistance (tone)			
Cutaneous, mucous membranes (α)	↑↑	↑↑	0
Skeletal muscle (β_2, α)	↑	↓ or ↑	↓ ↓
Renal (α, D_1)	↑	↑	↓
Splanchnic (α, β)	↑↑	↓ or ↑[1]	↓
Total peripheral resistance	↑↑↑	↓ or ↑[1]	↓ ↓
Venous tone (α, β)	↑	↑	↓
Cardiac			
Contractility (β_1)	0 or ↑	↑↑↑	↑↑↑
Heart rate (predominantly β_1)	↓ ↓ (vagal reflex)	↑ or ↓	↑↑↑
Stroke volume	0, ↓ , ↑	↑	↑
Cardiac output	↓	↑	↑↑
Blood pressure			
Mean	↑↑	↑	↓
Diastolic	↑↑	↓ or ↑[1]	↓ ↓
Systolic	↑↑	↑↑	0 or ↓
Pulse pressure	0	↑↑	↑↑


Norepinephrine
Epinephrine
Isoproterenol
PULSE RATE (min)
100
50
BLOOD PRESSURE (mm Hg)
180
120
60
10 µg/min
10 µg/min
10 µg/min
PERIPHERAL RESISTANCE
0
15
0
15
0
15
TIME (min)

Noncardiac Effects of Sympathomimetics

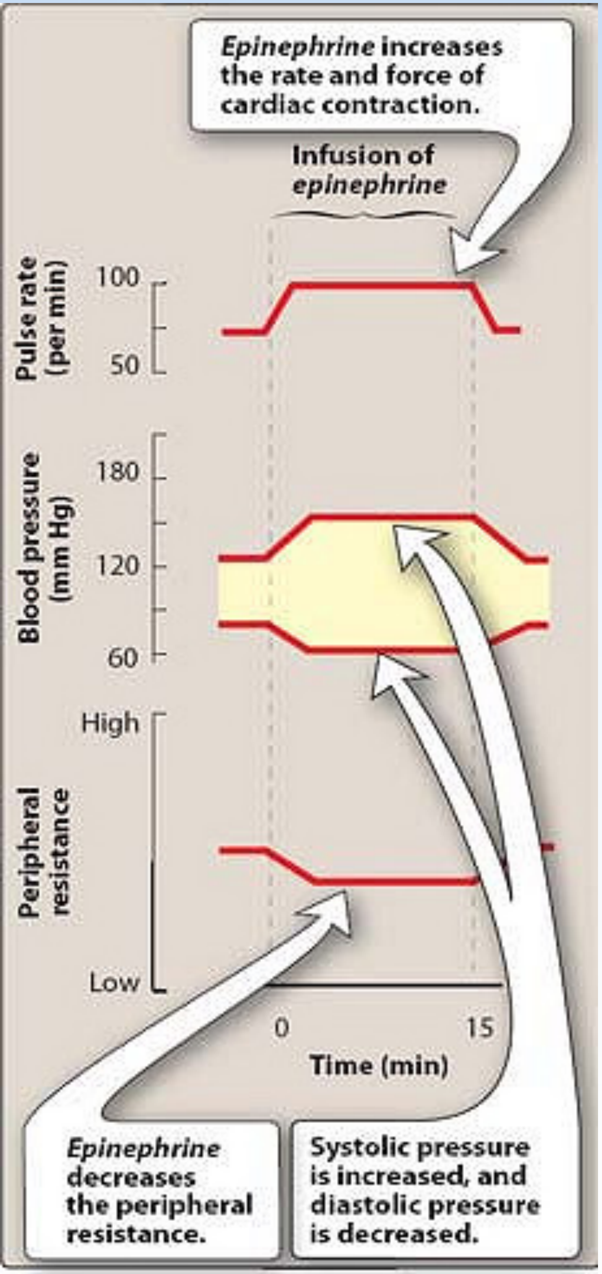
- bronchial smooth muscle
- genitourinary organs
- salivary glands
- apocrine sweat glands
- ……..

Sympathomimetics

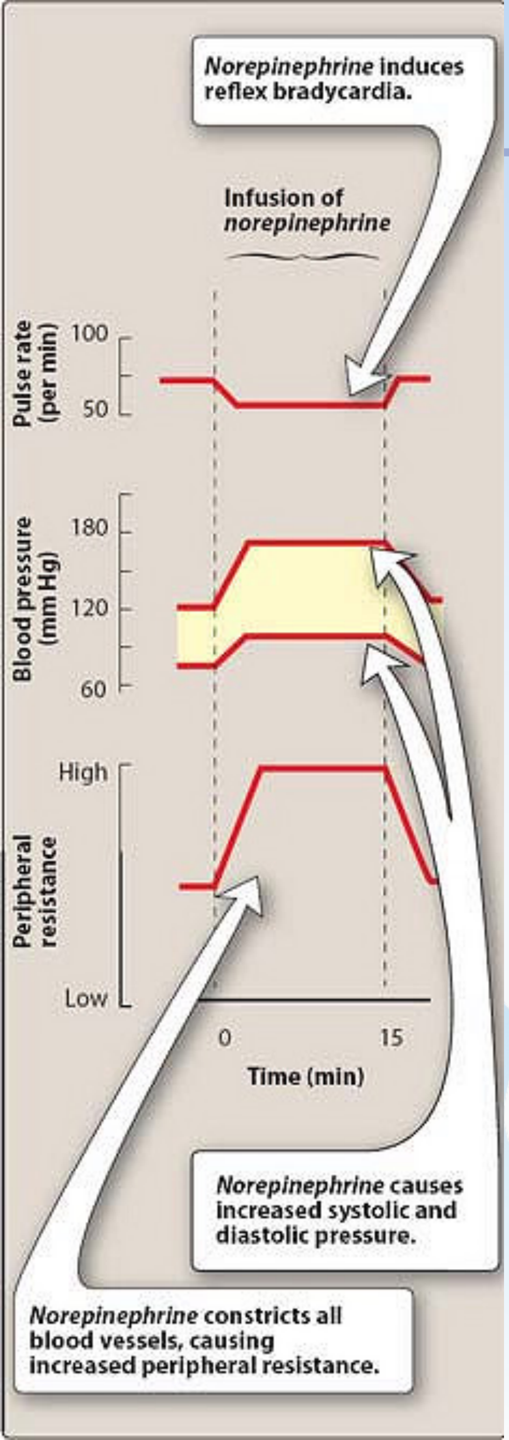
Endogenous Catecholamines

- Direct-acting
  - $\alpha_1 + \alpha_2$
    - Norepinephrine, epinephrine
  - α_1
    - Phenylephrine, Midodrine, Methoxamine, Naphazoline, oxymetazoline
  - α_2
    - Clonidine, moxonidine
  - $\beta_1 + \beta_2$
    - Isoproterenol, epinephrine
  - β_1
    - Dobutamine
  - β_2
    - Albuterol, terbutaline, metaproterenol, ritodrine
- Mixed-acting
  - Ephedrine, Phenylpropanolamine
- Indirect-acting
  - Amphetamine-Like: Amphetamine, Methylphenidate, Tyramine
  - Cocaine, Atomoxetine(Strattera®), Duloxetine, Sibutramine

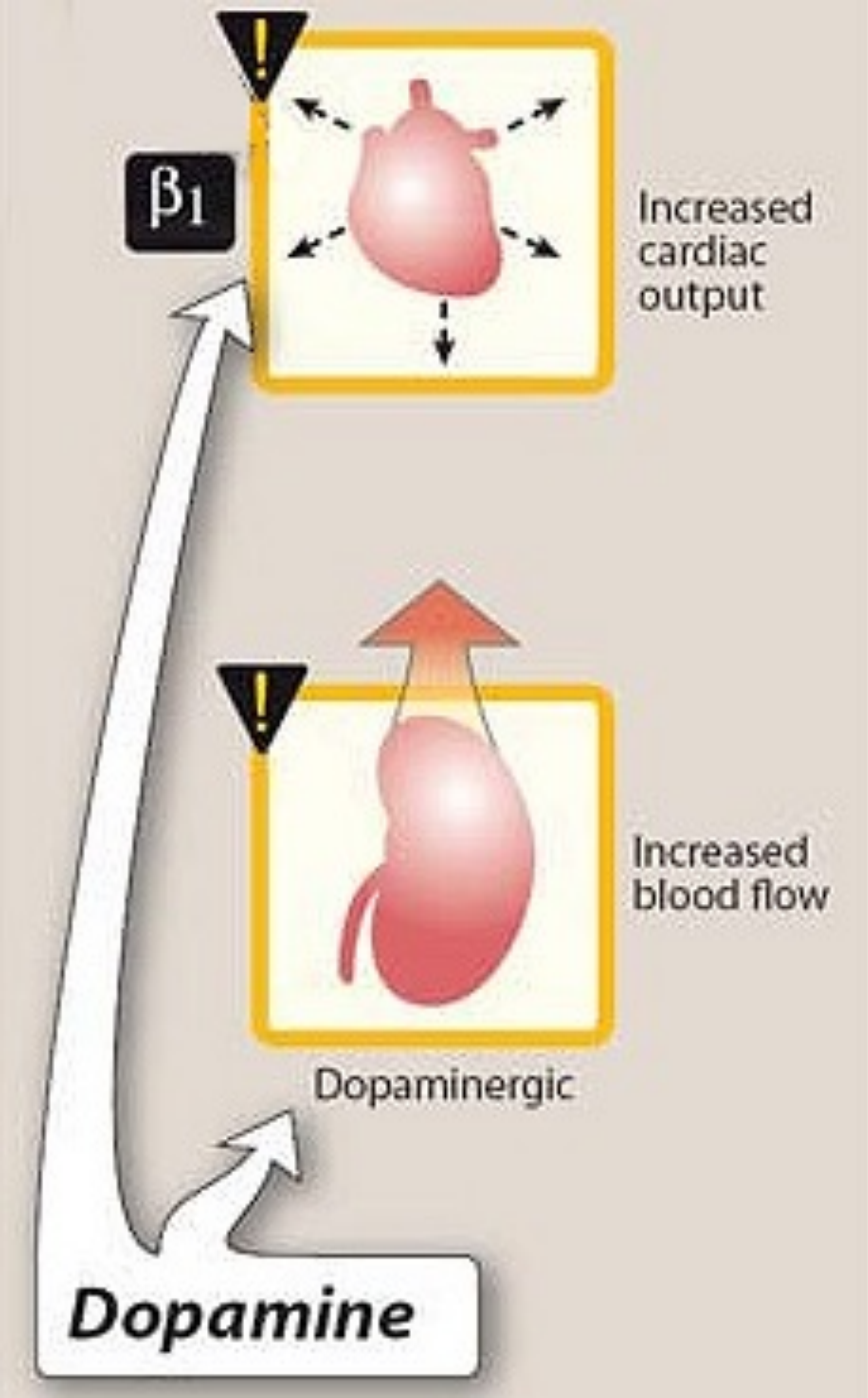
Specific Sympathomimetic Drugs



- Epinephrine, adrenaline (bosmin®)
  - mechanism
    - agonist at both α and β receptors
      - a very potent vasoconstrictor and cardiac stimulant
  - Actions
    - Cardiovascular
    - Respiratory
    - Hyperglycemia
    - Lipolysis
  - Clinical Applications
    - Anaphylaxis
      - Epinephrine is the drug of choice for the treatment of Type I hypersensitivity reactions in response to allergens.
    - Hemostatic
    - Anesthetics: Local anesthetic solutions usually contain 1:100,000 parts epinephrine
  - Toxicities (Adverse effects)
    - hypertension, arrhythmia, stroke, myocardial infarction, pulmonary edema



- Norepinephrine, noradrenaline (levophed®)
  - Mechanism
    - agonist at both α_1, α_2 >> β_1
  - Cardiovascular actions
    - Vasoconstriction
    - Baroreceptor reflex
  - Clinical Applications
    - Neurogenic shock; last resort therapy in shock
  - Toxicities (Adverse effects)
    - necrosis; excessive blood pressure increase, arrhythmias

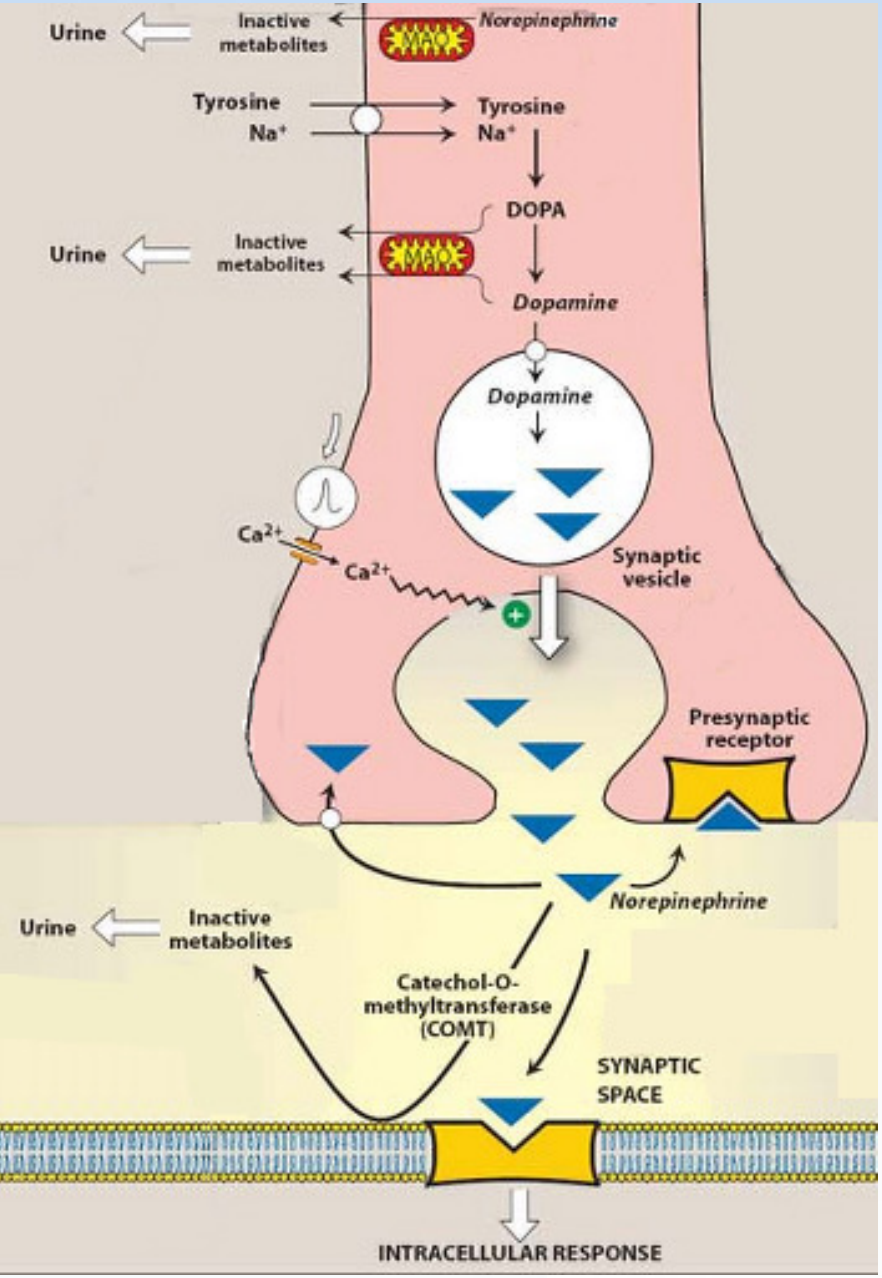


- Dopamine
  - Mechanism
    - D_1,β_1 (α_1) receptor
  - Actions
    - Cardiovascular
    - increasing blood flow to the kidneys
  - Clinical Applications
    - Shock
    - septic shock or cardiogenic shock
  - Toxicities (Adverse effects)
    - Cardiovascular disturbance, arrhythmias

Direct-Acting Sympathomimetics

- Direct-acting
  - $\alpha_1 + \alpha_2$
    - Norepinephrine, epinephrine
  - α_1
    - Phenylephrine, Midodrine, Methoxamine, Naphazoline, oxymetazoline
  - α_2
    - Clonidine, moxonidine, Dexmedetomidine
  - $\beta_1 + \beta_2$
    - Isoproterenol, epinephrine
  - β_1
    - Dobutamine
  - β_2
    - Albuterol, terbutaline, metaproterenol, ritodrine

Direct-acting -Phenylephrine

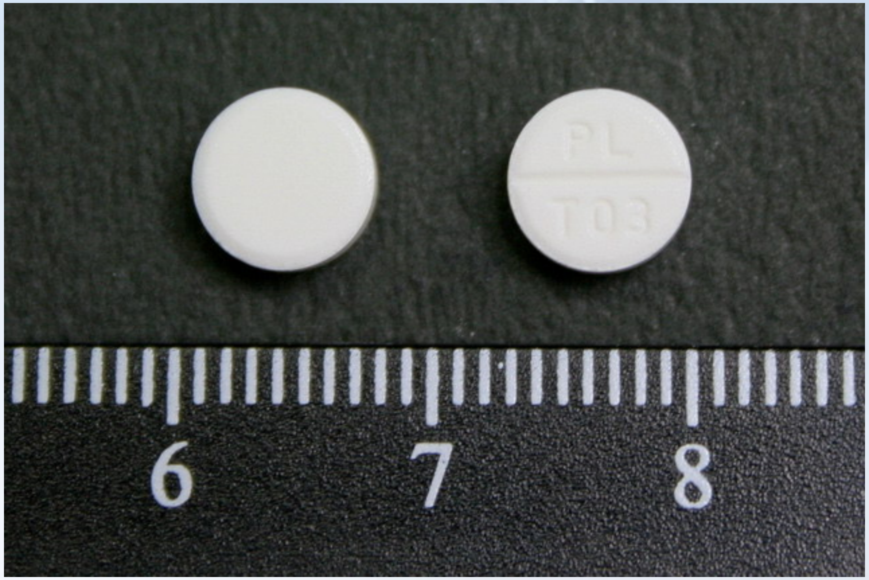


- Mechanism
  - pure α_1 agonist
    - not a catechol derivative
    - not inactivated by COMT
    - a longer duration of action than the catecholamines
- Clinical Applications
  - Mydriatic(散瞳劑)
  - Decongestant (充血解除劑)
- Toxicities (Adverse effects)
  - Hypertension, stroke, myocardial infarction

Direct-acting

Midodrine (midorine®)

- Mechanism
  - a selective α 1-receptor agonist
- Clinical Applications
  - orthostatic hypotension (typically due to impaired autonomic nervous system function)
- Toxicities (Adverse effects)
  - it may cause hypertension when the subject is supine (仰卧)



oxymetazoline

- Mechanism
  - direct-acting α agonists
- Actions
- Clinical Applications
  - decongestants
- Toxicities (Adverse effects)
  - 高血壓、緊張、噁心、頭暈、頭痛、 失眠及心悸等

Direct-acting

Clonidine (catapres®)

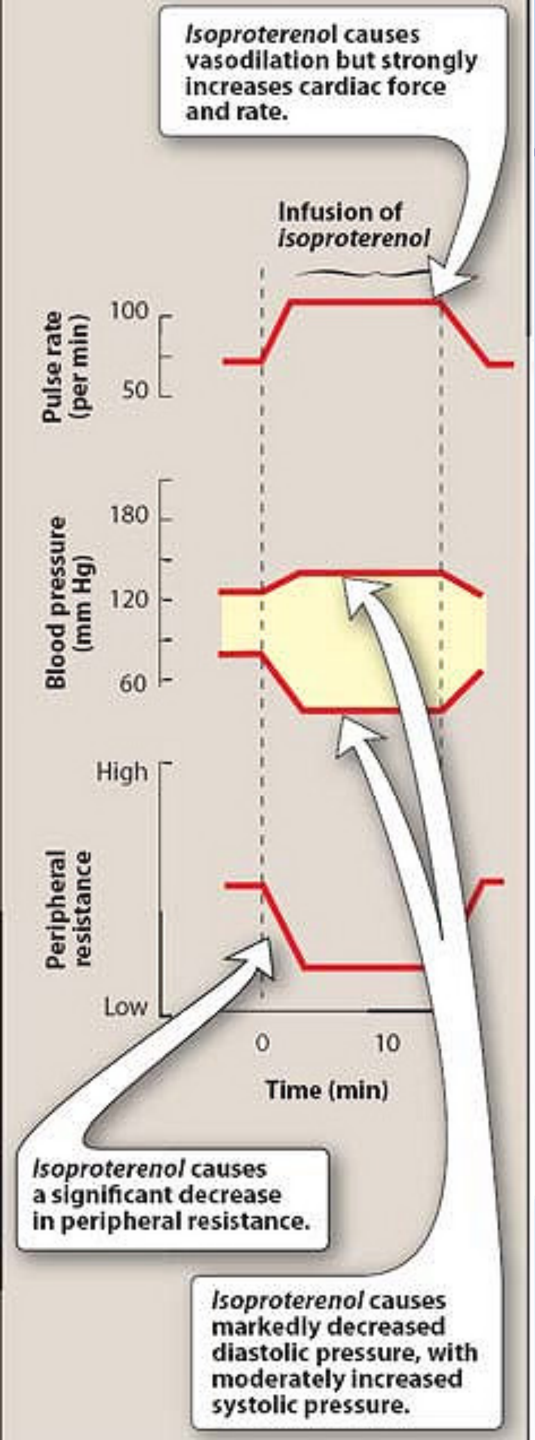
- Mechanism
  - α_2-receptor agonist
  - actions in the central nervous system
- Clinical Applications
  - be useful in the treatment of hypertension
- Toxicities (Adverse effects)
  - 口乾、鎮靜、嗜睡
  - Rebound hypertension

Direct-acting

Dexmedetomidine (Precedex®) Inj

- Mechanism
  - a centrally acting α_2-receptor agonist
- Clinical Applications
  - sedation
  - reduces the requirements for opioids in pain control
- Toxicities (Adverse effects)
  - 低血壓及心搏徐緩

- 中央健康保險局
  - 限用於短期可拔管之18歲以上外科病患，術後24小時內需鎮靜與止痛病患使用，且使用時間不得超過24小時。



Isoproterenol

- Mechanism
  - very potent β-receptor agonist
- Actions
  - Inotropic actions
  - A potent vasodilator
- Clinical Applications
  - primary use is in acute asthma, by nebulizer
- Toxicities (Adverse effects)

Dobutamine

- Mechanism (prenalterol與Dobutamine相同)
  - a partial β_1 agonist
  - less effective in activating vasodilator b2 receptors
- Actions
  - increase cardiac output with less reflex tachycardia than occurs with nonselective agonists such as isoproterenol
- Clinical Applications
  - Cardiogenic shock, acute heart failure
    - It is not routinely used in septic shock because it can lower systemic vascular resistance, thus leading to a risk of hypotension
- Toxicities (Adverse effects)
  - 增加心跳、血壓 、心悸、噁心、頭痛、胸痛…

Drug

- Albuterol, metaproterenol, terbutaline

- Mechanism
  - β_1 agonists
- Clinical Applications
  - for acute bronchospasm
- Toxicities (Adverse effects)
  - Tachycardia, tremor
  - glycemia↑

Ritodrine

- Mechanism
  - β_2 agonists
- Clinical Applications
  - treatment and prophylaxis of premature
- Toxicities (Adverse effects)
  - pulmonary edema, headache
  - glycemia↑
- Contraindication
  - contraindicated for use before the 20th week of pregnancy

Mixed-Acting Sympathomimetics

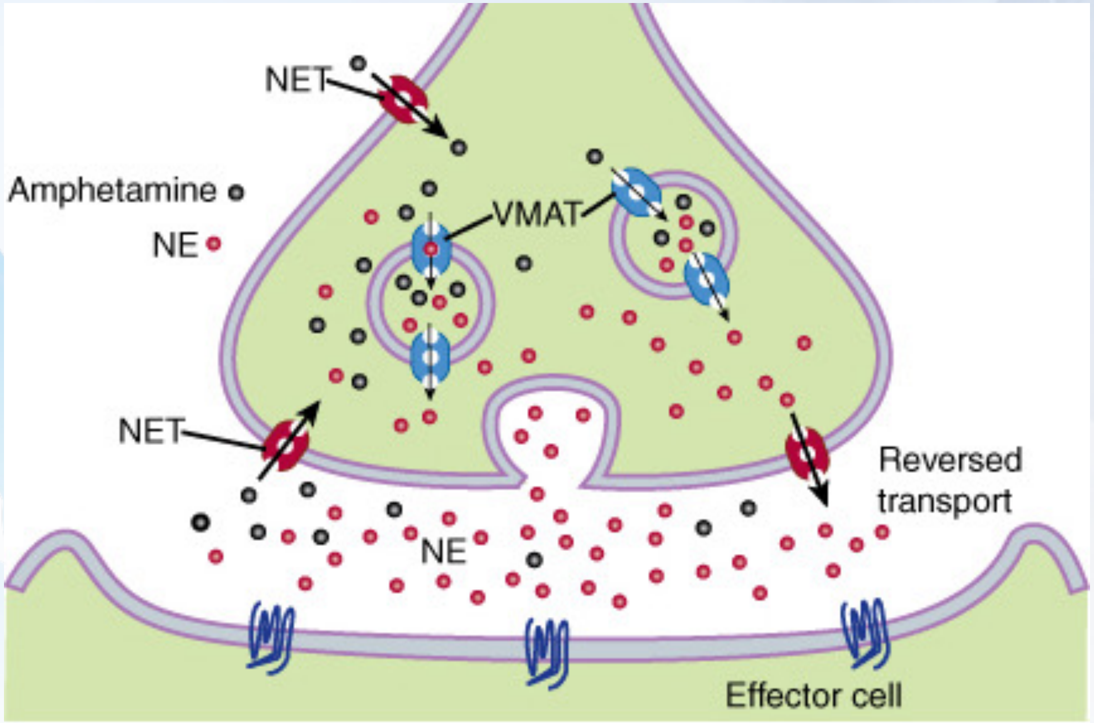
- Ephedrine
  - Mechanism
    - is both an α and a β receptor agonist
    - enhances release of norepinephrine from sympathetic neurons
  - Clinical Applications
    - Treatment of bronchial asthma, nasal congestion, acute bronchospasm
  - Toxicities (Adverse effects)
    - 血壓增高，心悸，顫抖，焦慮，心率不整
- Analogue
  - Pseudoephedrine, Phenylpropanolamine

Indirect-Acting Sympathomimetics

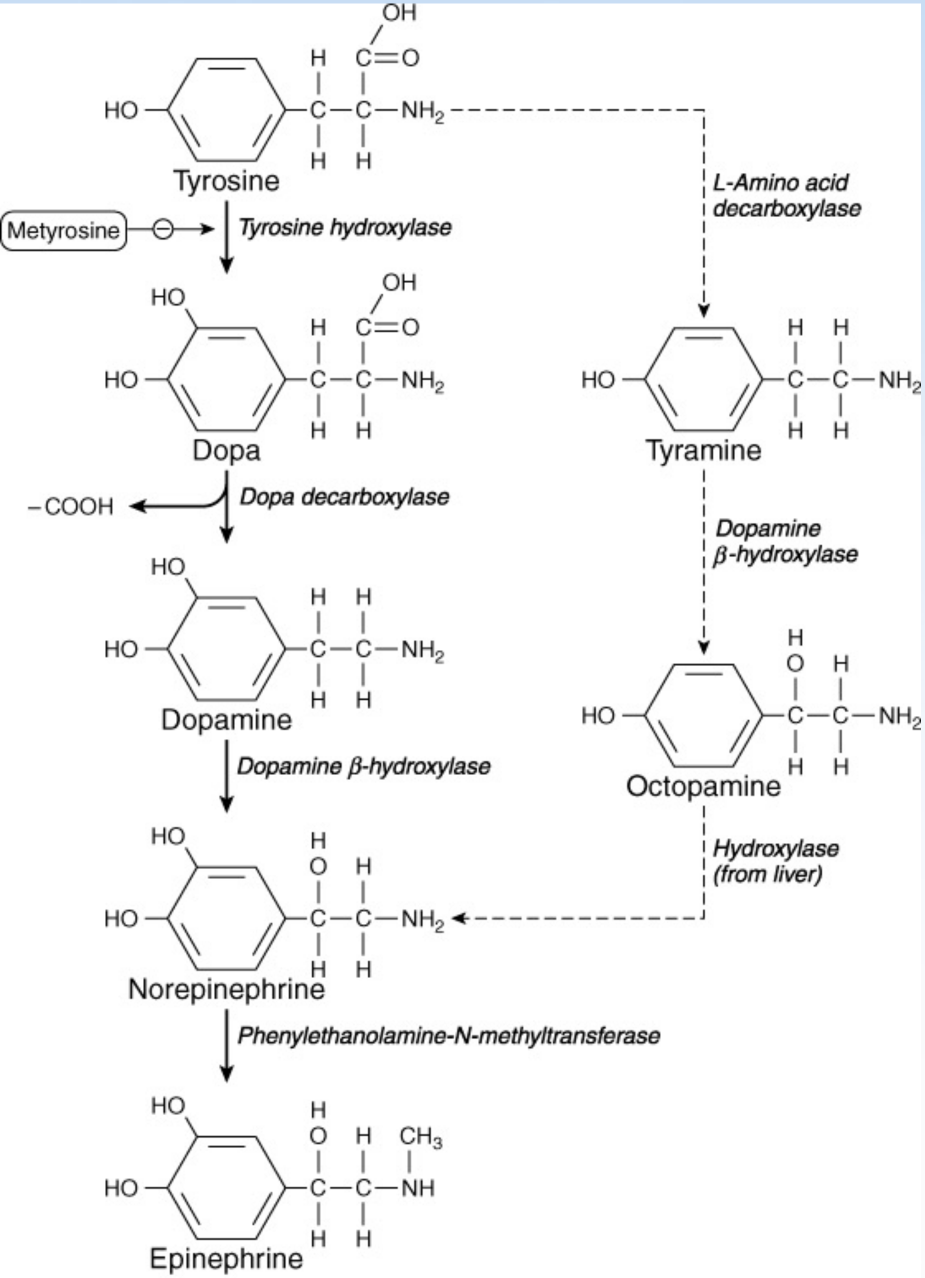
- Indirect-acting
  - Amphetamine-Like
    - Amphetamine, Methylphenidate, Tyramine
  - Cocaine, Atomoxetine (Strattera®), Duloxetine, Sibutramine

Amphetamine

- Mechanism
  - powerful CNS stimulant actions
  - release of norepinephrine (indirect-acting sympathomimetic drugs)
- Clinical Applications
  - Anorexiant (厭食), narcolepsy (嗜眠病) , ADHD (attention-deficit hyperactivity disorder)
- Toxicities (Adverse effects)
  - restlessness, dizziness, tremor, hyperactive reflexes, talkativeness, tenseness, irritability, weakness, insomnia, fever, and sometimes euphoria…



Tyramine

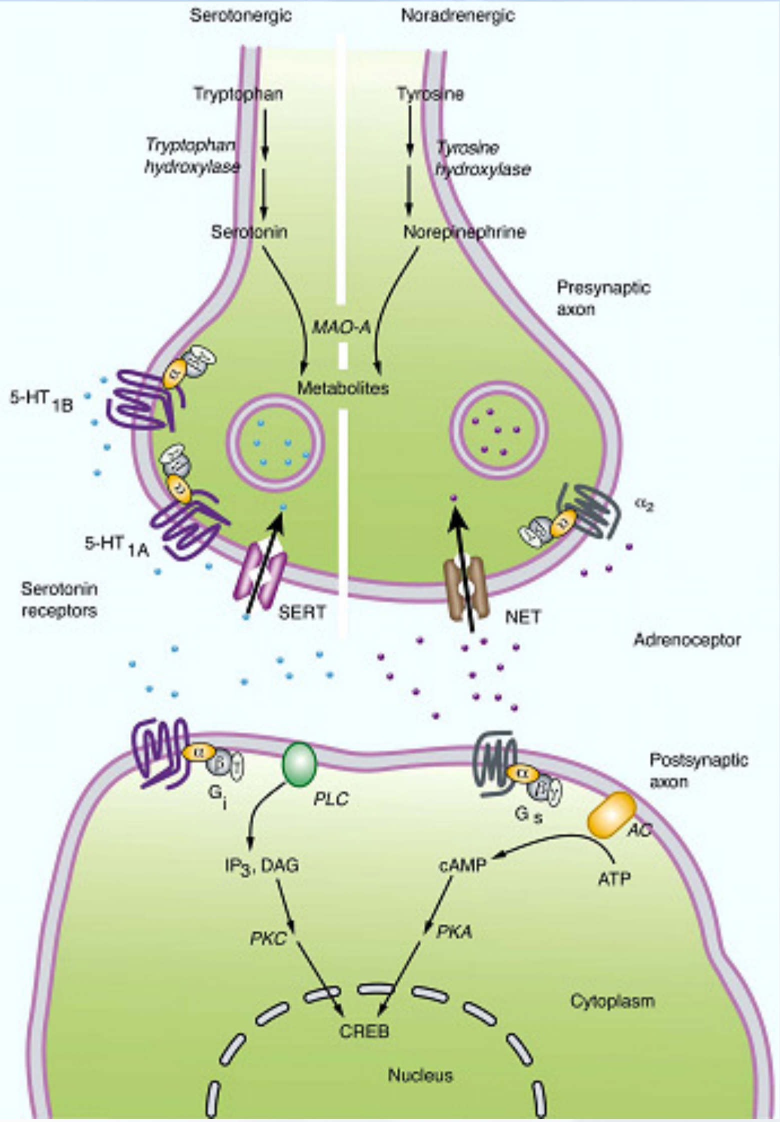


Tyramine

- is a normal by-product of tyrosine metabolism in the body and is also found in high concentrations in some fermented foods such as cheese

- Mechanism
  - If administered parenterally, it has an indirect sympathomimetic action caused by the release of stored catecholamines
  - tyramine's spectrum of action is similar to that of norepinephrine
- Interactions
  - Patients taking **MAO** inhibitors must be very careful to avoid tyramine-containing foods

- **Sibutramine**
- Mechanism
  – is a serotonin and norepinephrine reuptake inhibitor
- Clinical Applications
  – approved by the FDA for long-term treatment of obesity

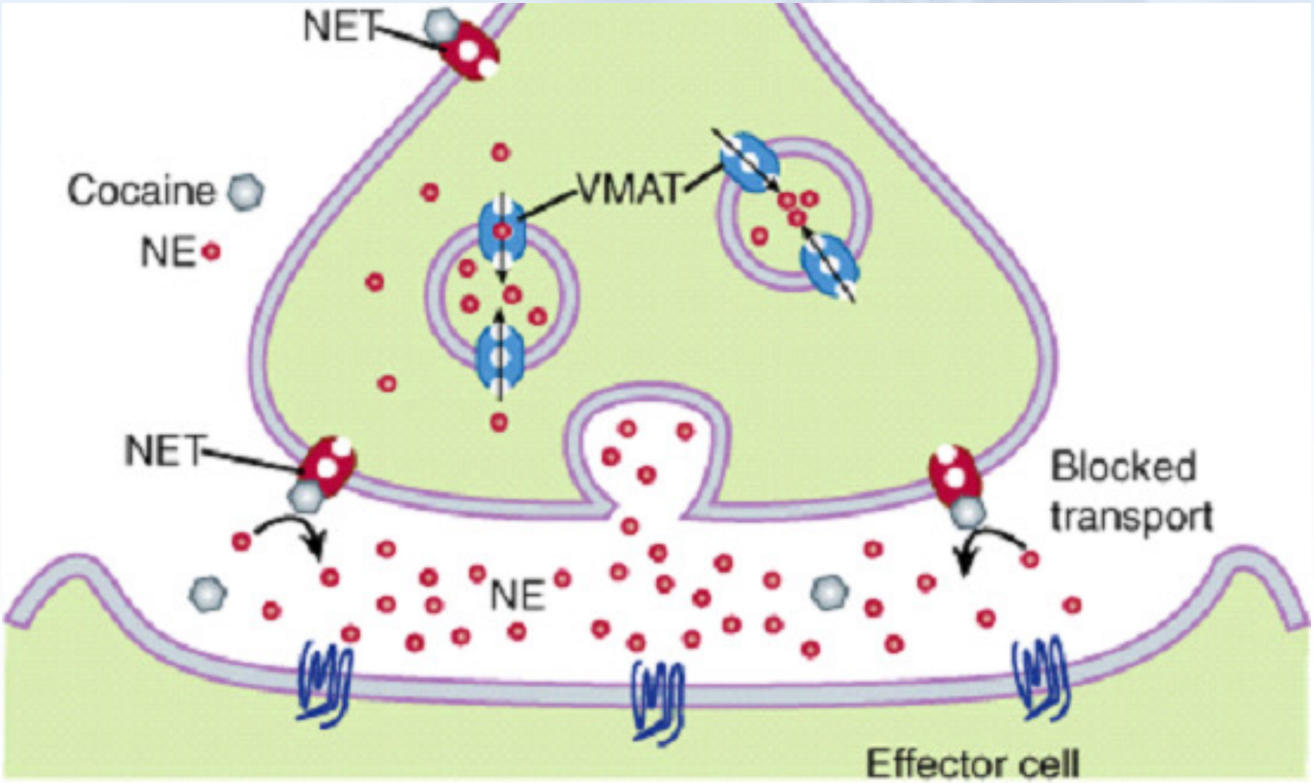


Atomoxetine (Strattera®)

- Mechanism
  - a selective inhibitor of the norepinephrine reuptake transporter
- Actions
  - a clonidine-like effect in the central nervous system to decrease sympathetic outflow while at the same time potentiating the effects of norepinephrine in the periphery.
- Clinical Applications
  - treatment of attention deficit disorders
- Toxicities (Adverse effects)
  - increase blood pressure
  - 胃腸不適、噁心、嘔吐、食慾降低、頭痛、暈眩…
- Interactions
  - 不宜與單胺氧化酶抑制劑（MAOI）及β2-agonist併用，可能會增加心臟毒性及副作用，因此需停用MAOI或β2-agonist兩週後才能服用atomoxetine

Cocaine

- Mechanism
  - peripheral sympathomimetic action
    - inhibition of transmitter reuptake at noradrenergic synapses
  - central nervous system
    - is to inhibit dopamine reuptake into neurons in the "pleasure centers" of the brain



Therapeutic Uses of Sympathomimetic Drugs

一. Cardiovascular Applications
二. Pulmonary Applications
三. Anaphylaxis(過敏性反應)
四. Ophthalmic Applications
五. Genitourinary Applications
六. Central Nervous System Applications
七. Additional Therapeutic Uses

一、Cardiovascular Applications

- Treatment of Acute Hypotension
  - Direct-acting α agonists such as
    - **norepinephrine**, **phenylephrine**, and **methoxamine**
- Cardiogenic shock and acute heart failure
  - usually due to massive myocardial infarction
  - Positive inotropic agents such as <u>**dopamine**</u> or <u>**dobutamine**</u> may provide short-term relief of heart failure symptoms in patients with advanced ventricular dysfunction (心功能障礙)

- Chronic Orthostatic Hypotension
- Cardiac Applications
  - complete heart block(完全性房室傳導阻斷)
  - cardiac arrest
- Inducing Local Vasoconstriction
  - Occasionally, cocaine is mixed with epinephrine for maximum hemostasis and local anesthesia
  - phenylephrine is often used in nasal decongestant sprays

- 二、Pulmonary Applications
- 三、Anaphylaxis(過敏性反應)
  - – Anaphylactic shock and related immediate (type I) IgE-mediated reactions

  ⬇ affect both the respiratory and the cardiovascular systems

  ⬇rapidly i.v. **epinephrine,** 0.3–0.5 mg (0.3–0.5 mL of a 1:1000 epinephrine solution)

    ⇨**may be the preferred route of administration**

- 四、Ophthalmic Applications
  - Examination of the retina
    - Phenylephrine is an effective mydriatic agent
  - Horner's syndrome
    - Sympathomimetics administered as ophthalmic drops are also useful in it
  - glaucoma
    - **Apraclonidine** and **brimonidine** are α2-selective agonists→intraocular pressure ⬇
- 五、Genitourinary Applications
  - relax the pregnant uterus
    - **Ritodrine, terbutaline**

六、Central Nervous System Applications

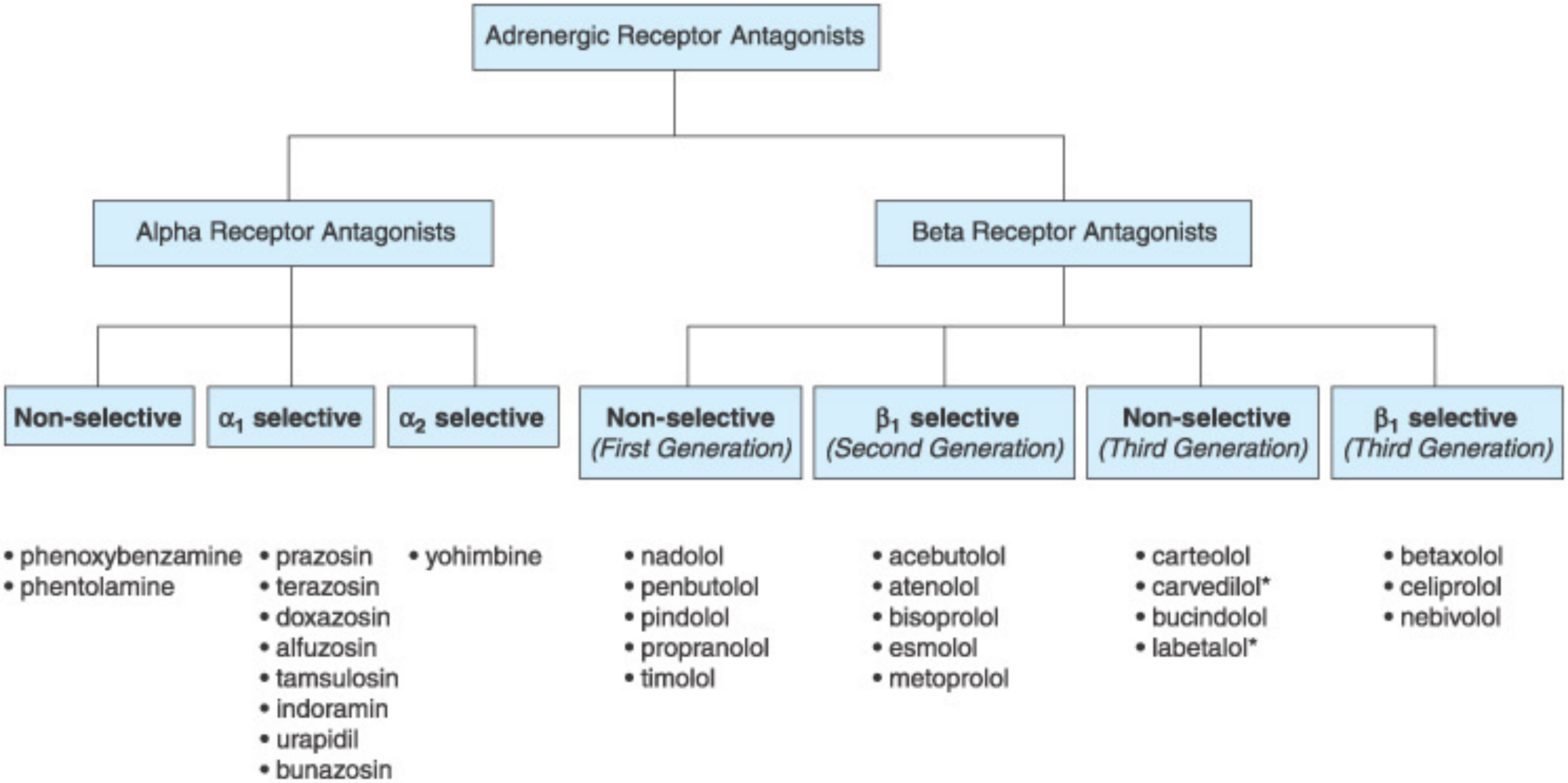
- in the treatment of narcolepsy
  - **Modafinil,** a new amphetamine substitute, is approved for use in **narcolepsy** and is claimed to have fewer disadvantages (excessive mood changes, insomnia and abuse potential) than amphetamine in this condition
- attention-deficit hyperactivity disorder (ADHD)
  - **methylphenidate**

七、Additional Therapeutic Uses

- clonidine
  - diminishing craving for narcotics and alcohol during withdrawal syndrome
  - diminish menopausal hot flushes
- Dexmedetomidine
  - is an α_2 agonist used for sedation under intensive care circumstances and during anesthesia
- Tizanidine
  - is an α_2 agonist that is used as a muscle relaxant

Chapter 10.

Adrenoceptor Antagonist Drugs

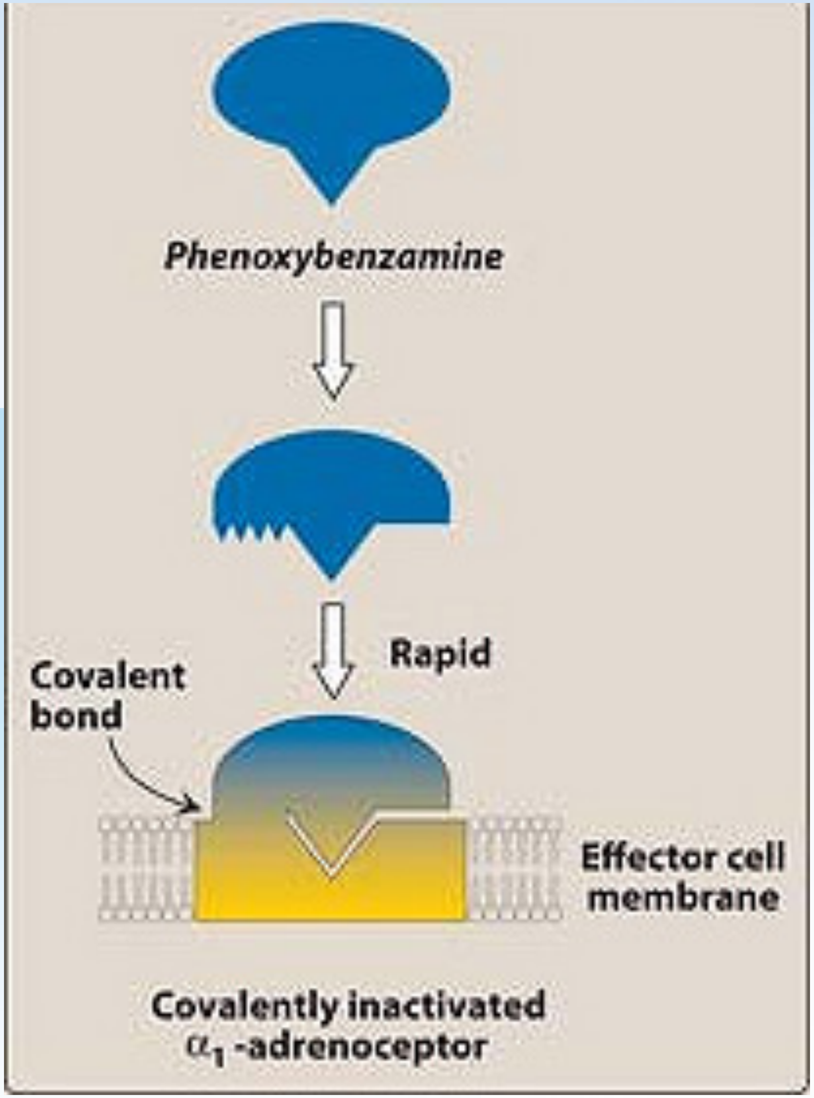


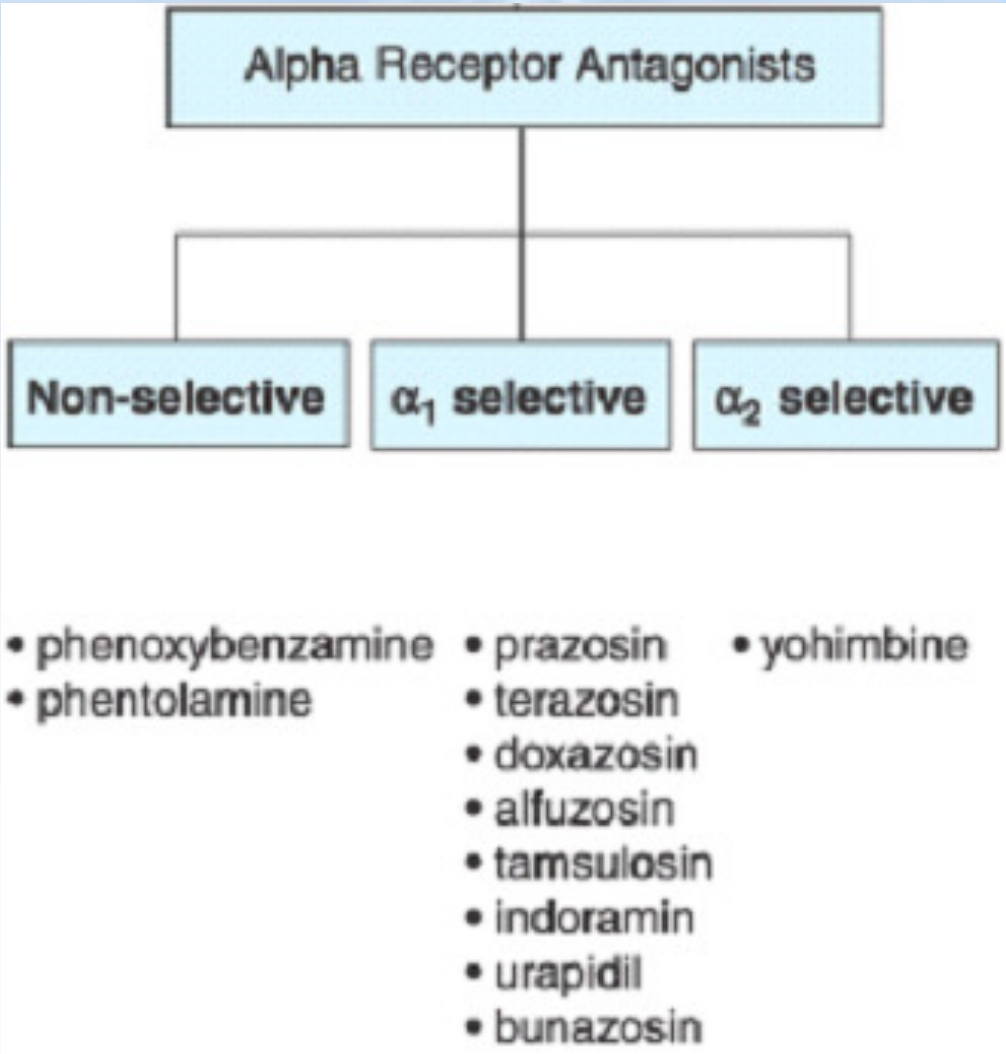
<u>Cental & peripheral acting sympatholytics</u>

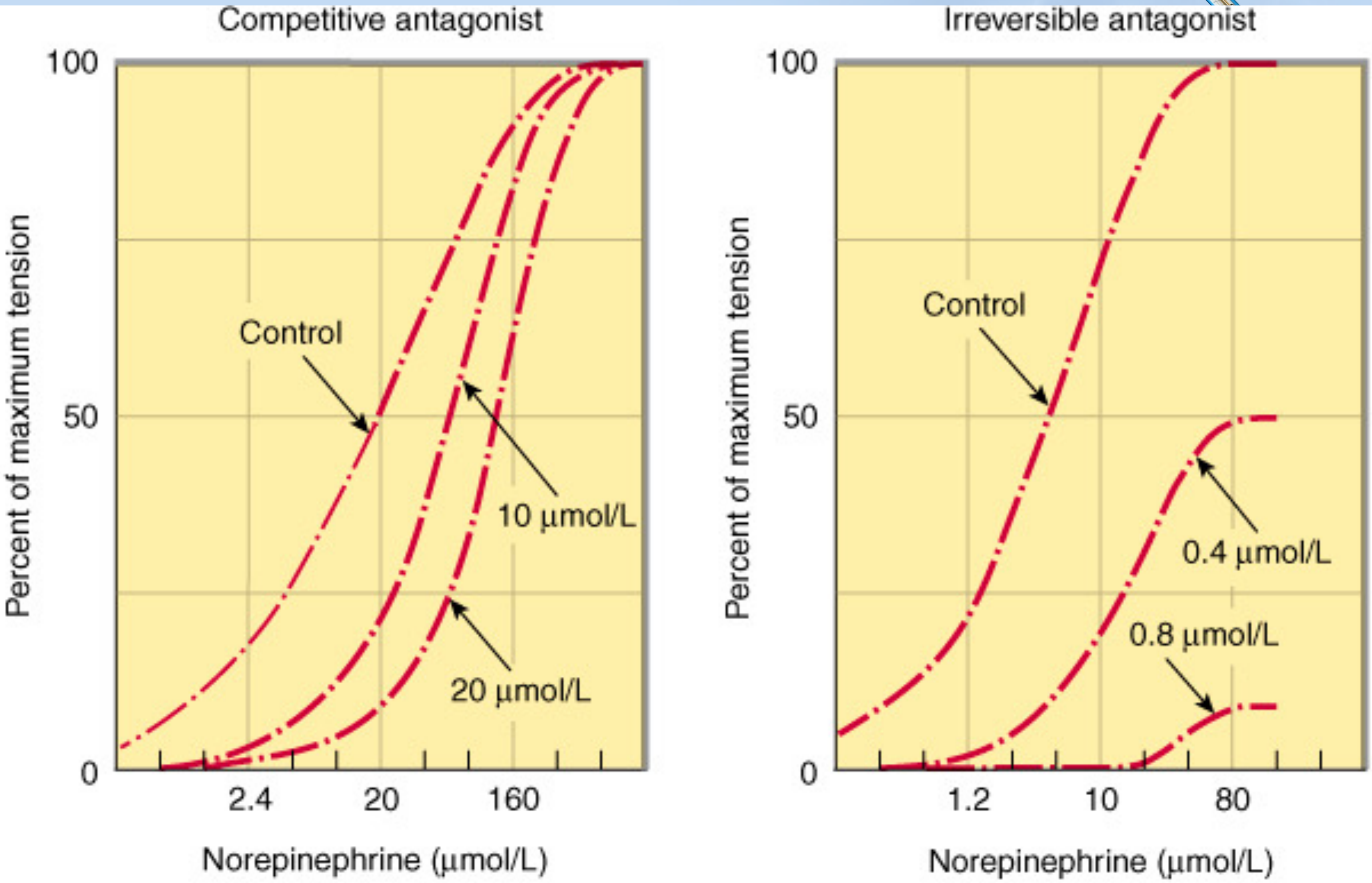
- Clonidine
- Guanethidine, Guanfacine
- Methyldopa
- Reserpine

Basic Pharmacology of the Alpha-Receptor Antagonist Drugs

- Mechanism of Action







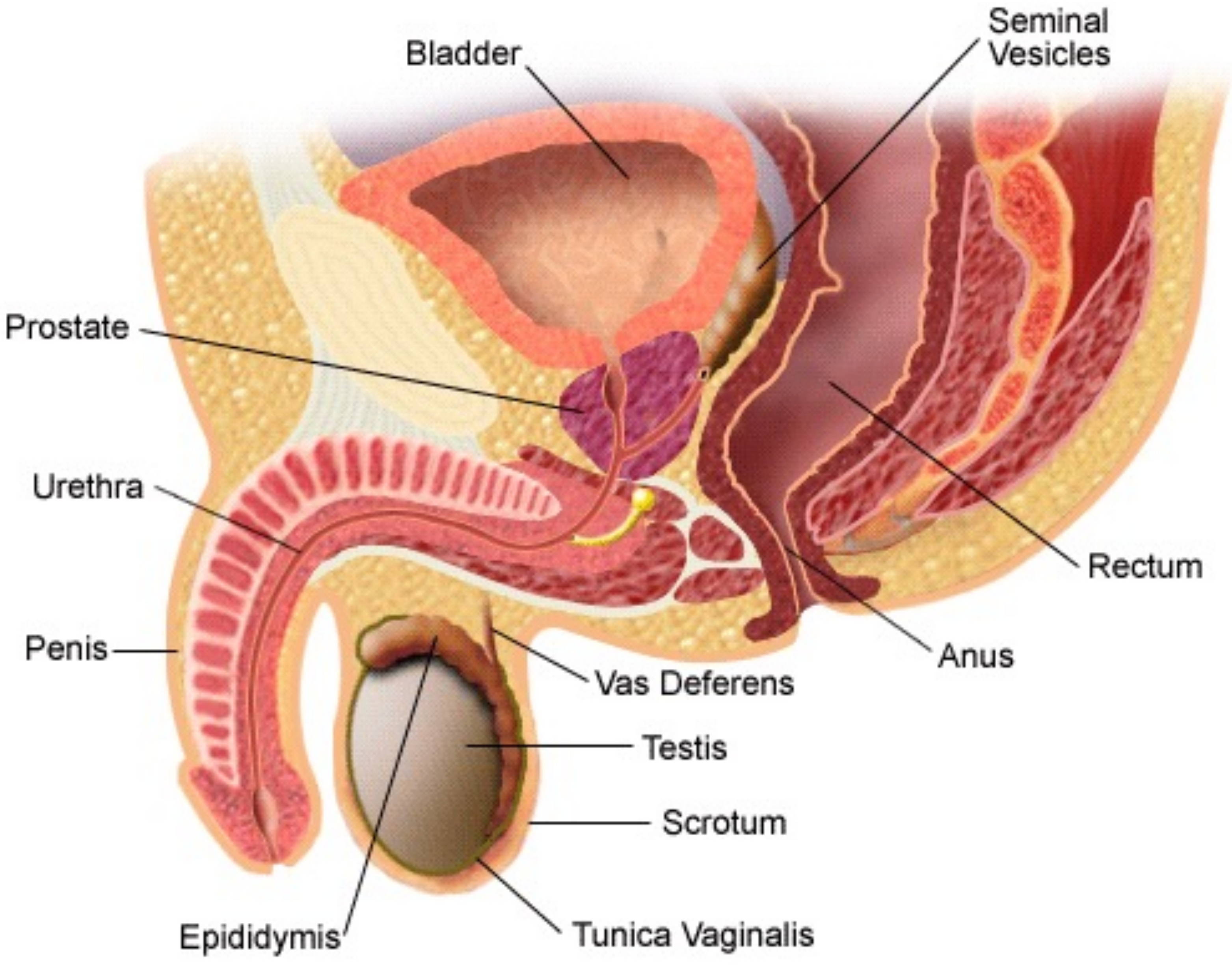
Competitive antagonist
100
50
0
Control
10 µmol/L
20 µmol/L
2.4
20
160
Percent of maximum tension
Norepinephrine (µmol/L)
Irreversible antagonist
100
50
0
Control
0.4 µmol/L
0.8 µmol/L
1.2
10
80
Percent of maximum tension
Norepinephrine (µmol/L)

	Receptor Affinity
<u>Alpha antagonists</u>	
Prazosin, terazosin, doxazosin	$\alpha_1 >>>> \beta_2$
Phenoxybenzamine	$\alpha_1 > \beta_2$
Phentolamine	$\alpha_1 = \beta_2$
Yohimbine, tolazoline	$\alpha_2 >> \beta_1$
<u>Mixed antagonists</u>	
Labetalol, carvedilol	$\beta_1 = \beta_2 \geqq \alpha_1 > \alpha_2$
<u>Beta antagonists</u>	
Metoprololol, **<u>acebutolol</u>**, alprenolol, **<u>atenolol</u>**, betaxolol, celiprolol, esmolol, nebivolol	$\beta_1 >>> \beta_2$
Propranolol, carteolol, penbutolol, **<u>pindolol</u>**, **<u>timolol</u>**, **<u>Nadolol</u>**	$\beta_1 = \beta_2$
Butoxamine	$\beta_2 >>> \beta_1$

Pharmacologic Effects α receptor anatgonist

- Cardiovascular Effects
  - Alpha-receptor antagonists often cause orthostatic hypotension and reflex tachycardia
    - Orthostatic hypotension is due to antagonism of sympathetic nervous system stimulation of α_1 receptors in vascular smooth muscle
    - tachycardia may be more marked with
      - block α_2-presynaptic receptors $\rightarrow$NE$\uparrow$ $\rightarrow$stimulate β receptors
- Other Effects
  - miosis
  - nasal stuffiness(鼻塞)
  - treatment $\rightarrow$prostatic hyperplasia

Male Reproductive Tract



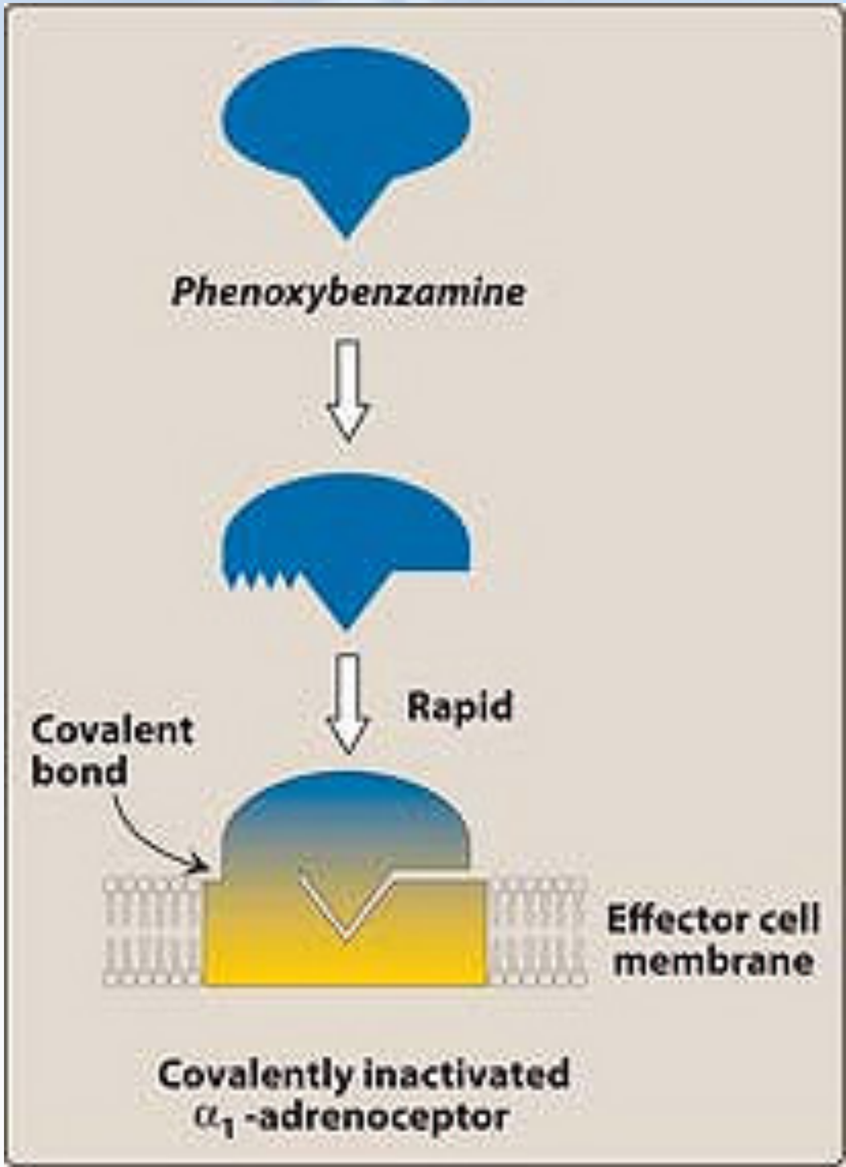
攝護腺肥大症狀評估表	都沒有	五次小便中少於一次有此情況	少於半數的小便次數中有此情況	大約有半數的小便次數中有此情況	半數以上的小便次數中有此情況	差不多經常如此	患者症狀的評估
膀胱不能完全排盡尿液：在過去一個月，每當您小便完時，您感到膀胱裡的尿液並未完全排盡的次數是	0	1	2	3	4	5	
排尿的次數：在過去一個月，每當您小便完兩小時內，您又頻頻想小便的次數是	0	1	2	3	4	5	
間歇尿症狀:在過去一個月,每當您小便完時,您發現您的小便斷斷續續次數是	0	1	2	3	4	5	
尿急的症狀:在過去一個月,您覺得無法憋尿的次數是	0	1	2	3	4	5	
排尿無力的症狀:在過去一個月,您覺得排尿無力尿弱的次數是	0	1	2	3	4	5	
逼尿的症狀:在過去一個月,您覺得開始排尿時必須用逼尿才能排出的次數是	0	1	2	3	4	5	
夜尿症 :在過去一個月,由您開始上床直至早上睡醒時您為了小便要起床的次數是	沒有	一次	二次	三次	四次	五次以上	

總分數：

0-7分表示症狀輕微
8-9分表示症狀中等
20-35分表示症狀嚴重

Phenoxybenzamine

- Mechanism
  - binds covalently to α receptors
- Actions
  - related to antagonism of α-receptor–mediated events
    - The most significant effect is attenuation of catecholamine-induced vasoconstriction
- Clinical Applications
  - In the treatment of pheochromocytoma (嗜鉻細胞瘤)
- Toxicities (Adverse effects)
  - orthostatic hypotension and tachycardia

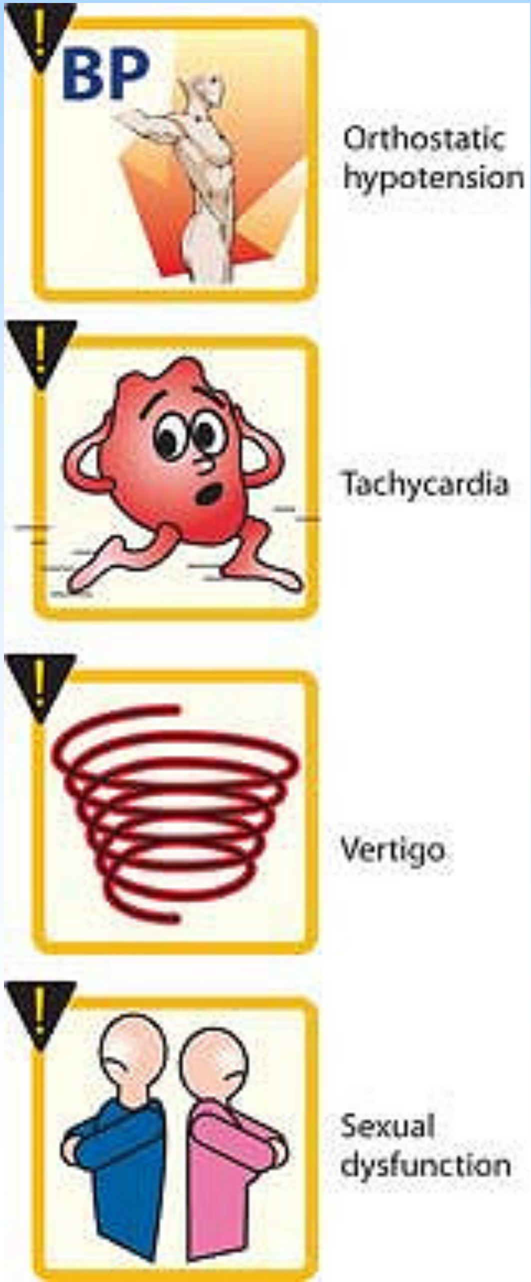


Phentolamine

- Mechanism
  - a potent competitive antagonist at both α_1 and α_2 receptors
- Actions
  - cardiac stimulation → antagonism of presynaptic α_2 receptors
    - leading to enhanced release of norepinephrine from sympathetic nerves
  - sympathetic activation from baroreflex mechanisms
- Clinical Applications
  - in the treatment of pheochromocytoma
    - used for the treatment of impotence (before)
- Toxicities (Adverse effects)
  - severe tachycardia, arrhythmias, and myocardial ischemia

Prazosin (Minipress®) Terazosin Doxazosin Tamsulosin

- Mechanism
  - highly selective for α_1 receptors
- Actions
  - relaxes both arterial and venous vascular smooth muscle, as well as smooth muscle in the prostate
- Clinical Applications
  - Hypertension
  - benign prostatic hyperplasia (Tamsulosin, Alfuzosin)
- Toxicities (Adverse effects)
  - Orthostatic hypotension
  - reflex tachycardia



新包裝
PRESCRIPTION MEDICINE
KEEP OUT OF REACH OF CHILDREN
Minipress
1mg
PRAZOSIN TABLETS
Pfizer
請置於兒童無法取得處
脈寧平
1公絲
錠
100錠
PRAZOSIN TABLETS
Pfizer

舊包裝
PRESCRIPTION ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN
Minipress
1mg
PRAZOSIN TABLETS
Pfizer
PRESCRIPTION ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN
脈寧平
1公絲
錠
100錠
PRAZOSIN TABLETS
Pfizer

MNP 1
PFI ZER
cm
1
2
3
Minipress 1mg Pfizer

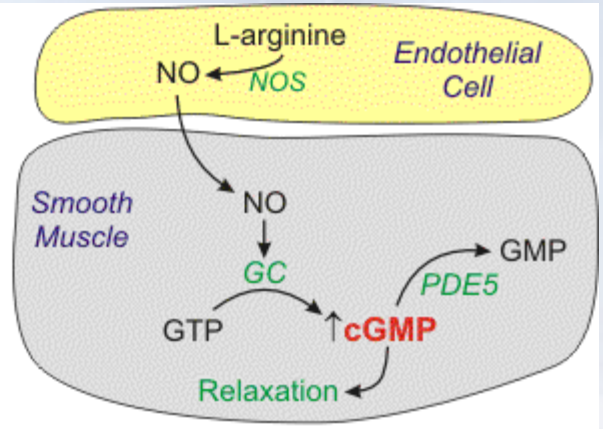
Tamsulosin

Compared with other antagonists, tamsulosin has less effect on standing blood pressure in patients.

置於舌上,待藥品溶解後吞下

Other Alpha-Adrenoceptor Antagonists

- Labetalol
  - has both α_1-selective and -β antagonistic effects
- Ergot derivatives
  - ergotamine and dihydroergotamine, cause reversible a-receptor blockade, probably via a partial agonist action (5-HT, dopamine)
- Yohimbine
  - an indole alkaloid, is an a2-selective antagonist
  - It was once widely used to improve male erectile dysfunction but has been superseded by phosphodiesterase-5 inhibitors like sildenafil



Abbreviations: NO, nitric oxide; NOS, nitric oxide synthase; GC, guanylyl cyclase; PDE5, cGMP-dependent phosphodiesterase (type 5)

- Pheochromocytoma
  - is a tumor of the adrenal medulla or sympathetic ganglion cells. The tumor secretes catecholamines, especially norepinephrine and epinephrine
  - symptoms
    - hypertension, headaches, palpitations, and increased sweating
  - The major clinical use of phenoxybenzamine is in the management of pheochromocytoma

Clinical Pharmacology(2) Alpha-Receptor–Blocking Drugs

- Hypertensive Emergencies
  - The α-adrenoceptor antagonist drugs have limited application in the management of hypertensive emergencies, but labetalol has been used in this setting
- Chronic Hypertension
  - Members of the prazosin family of α_1-selective antagonists are efficacious drugs in the treatment of mild to moderate systemic hypertension
  - they are **not** usually recommended as **monotherapy** for hypertension
  - Orthostatic hypotension should be checked routinely in any patient

Clinical Pharmacology(3) Alpha-Receptor–Blocking Drugs

- Peripheral Vascular Disease
- Urinary Obstruction
  - Prazosin, doxazosin, and terazosin are all efficacious in patients with BPH
  - tamsulosin
    - is also efficacious in BPH
      - may be preferred in patients who have experienced orthostatic hypotension with other α_1-receptor antagonists

- Erectile Dysfunction

phentolamine + papaverine → erection → fibrotic reactions

- Alternative therapies for erectile dysfunction include
  ⇨prostaglandins, sildenafil, apomorphine

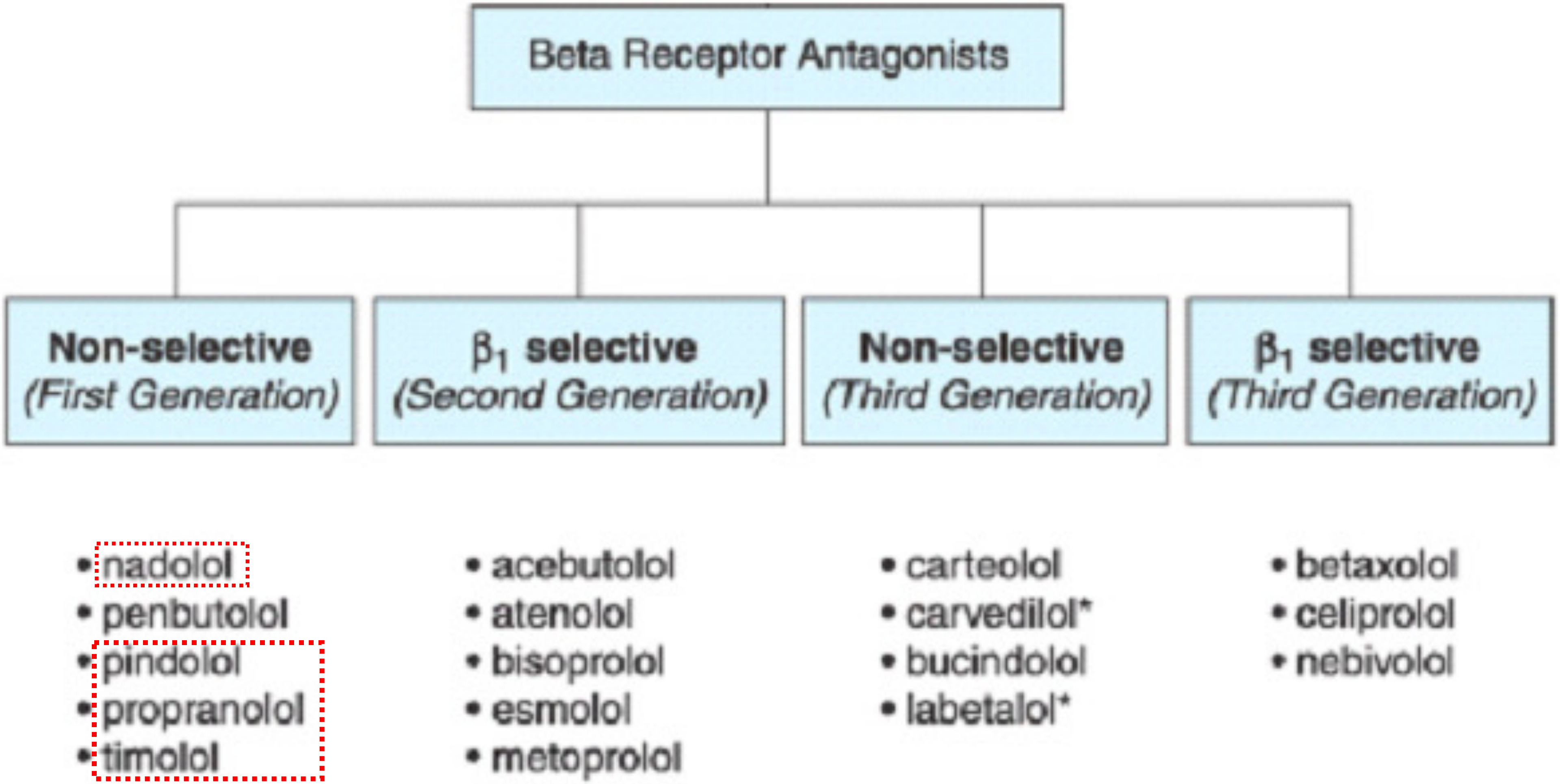
Applications of Alpha2 Antagonists

Alpha2 antagonists have relatively little clinical usefulness. They have limited benefit in male erectile dysfunction

- α-blocker優點
  - α-blocker 主要是對血管收縮產生抑制作用,使血管擴張而達到降血壓目的
  - 不會影響葡萄糖耐受性
  - 心衰竭病患可使用
  - 氣喘亦可使用

- α-blocker side effect
  - 姿態性血壓
  - 反射性心跳加速
  - 頭暈
  - 性無能

Beta-Receptor Antagonists



Pharmacokinetic Properties of the Beta-Receptor Antagonists

	Selectivity	Partial Agonist Activity	Local Anesthetic Action	Elimination Half-life
Acebutolol	β_1	Yes	Yes	3–4 hours
Atenolol	β_1	No	No	6–9 hours
Betaxolol	β_1	No	Slight	14–22 hours
Bisoprolol	β_1	No	No	9–12 hours
Carteolol	None	Yes	No	6 hours
Carvedilol	None	No (cause α_1-adrenoceptor blockade)	No	7–10 hours
Celiprolol	β_1	Yes	No	4–5 hours
Esmolol	β_1	No	No	10 minutes
Labetalol	None	Yes (cause α_1-adrenoceptor blockade)	Yes	5 hours
Metoprolol	β_1	No	Yes	3–4 hours
Nadolol	None	No	No	14–24 hours
Nebivolol	β_1	?[2]	No	11–30 hours
Penbutolol	None	Yes	No	5 hours
Pindolol	None	Yes	Yes	3–4 hours
Propranolol	None	No	**Yes**	3.5–6 hours
Sotalol	None	No	No	12 hours
Timolol	None	No	No	4–5 hours

- 具有內生性擬交感神經活性(intrinsic sympathomimetic activity, ISA)，適於心跳遲緩或有糖尿病的高血壓患者

Advantages of ISA

- Less Bronchospasm
- Less Peripheral blood flow
- No increase in peripheral resistance
- Less risk of CHF
- Less bradycardia
- Less risk of withdrawal syndrome

ISA Beta-blockers *v.s.* Beta 1-selective blockers

ISA Beta-blockers 的優點	Beta 1-selective blockers 的優點
Less bradycardia	
Less risk of congestive heart failure	
Less bronchospasm	Less bronchospasm
No increase in peripheral resistance	Less increase in peripheral resistance
Less worsening of peripheral vascular disease	Less decrease in peripheral blood flow
No effect in diabetic control	No effects in Diabetic control
Less risk of withdrawal syndrome	

- β -Adrenergic antagonists
  - Propranolol (Inderal®)
  - Timolol
  - Nadolol (Corgard®)
  - Pindolol (Visken®) ^{ISA}
  - Carteolol ^{ISA}
  - Penbutolol ^{ISA}
- β_1-Adrenergic antagonists
  - Acebutolol ^{ISA}
  - Atenolol (Tenormin®) ^{ISA}
  - Metoprolol
- β -Adrenergic antagonists with ISA (Intrinsic sympathomimetic activity)
  - Acebutolol
  - Atenolol (Tenormin®)
  - Carteolol
  - Pindolol (Visken®)
  - Penbutolol
- Mix adrenergic antagonists
  - Labetalol (Trandate®)

Pharmacodynamics of the Beta-Receptor Antagonist Drugs

- Effects on the Cardiovascular System
  - *not* usually cause hypotension in healthy individuals with normal blood pressure
  - In the treatment of
    - angina
    - chronic heart failure
    - myocardial infarction
    - arrhythmias
- Effects on the Respiratory Tract
  - Blockade of the β_2 receptors

→airway resistance ⬆

→asthma ⬆

Effects on the Eye The Treatment of Glaucoma

	Mechanism
Cholinomimetics Pilocarpine, carbachol, physostigmine, echothiophate, demecarium	Ciliary muscle contraction, opening of trabecular meshwork; increased outflow
Alpha agonists Nonselective Epinephrine, dipivefrin	Increased outflow
Alpha$_2$-selective Apraclonidine Brimonidine	Decreased aqueous secretion
Beta-blockers Timolol, betaxolol, carteolol, levobunolol, metipranolol	Decreased aqueous secretion from the ciliary epithelium
Diuretics Dorzolamide, brinzolamide, Acetazolamide, dichlorphenamide, methazolamide	Decreased aqueous secretion due to lack of HCO_3^-
Prostaglandins Latanoprost, bimatoprost, travoprost, unoprostone	Increased outflow

- Metabolic and Endocrine Effects
  - inhibit → lipolysis
  - inhibit → glycogenolysis
  - VLDL⬆ , HDL⬇
- Effects Not Related to Beta-Blockade
  - Partial β-agonist activity
    - intrinsic sympathomimetic activity→Pindolol
    - asthma ⬇ or bradycardia ⬇

Specific Agents

Propranolol

- Mechanism
  - the prototypical β-blocking drug
    - **Nonselective β blockers**
- Actions
  - Lower HR and BP reduce renin
- Clinical Applications
  - Angina, arrhythmias (treatment and prophylaxis), hypertension, tremor, stage fright(緊張不安), migraine
- Toxicities (Adverse effects)
  - bronchospasm (can be fatal in asthmatics), atrioventricular block, heart failure; CNS sedation, lethargy(無精打采), sleep disturbances

- Nonselective β blockers
  - Timolol, betaxolol
    - Lack local anesthetic action; useful in glaucoma
  - Pindolol
    - Partial agonist action; possibly safer in asthma
  - Nadolol
    - Like propranolol but longer action (up to 24 h) and less CNS effect

intrinsic sympathomimetic activity (ISA)

- Drug
  - Pindolol, acebutolol, carteolol, and penbutolol
- Mechanism
  - β_1, β_2, with intrinsic sympathomimetic (partial agonist) effect
- Actions
  - Lowers BP, modestly lower HR
- Clinical Applications
  - Hypertension, arrhythmias, migraine
  - may avoid worsening of bradycardia
- Toxicities (Adverse effects)
  - Fatigue, vivid dreams, cold hands

Clinical Pharmacology of the β Receptor Blocking Drugs

- Hypertension
- Ischemic Heart Disease
- Cardiac Arrhythmias
- Heart Failure
- Other Cardiovascular Disorders
- Glaucoma
- Hyperthyroidism
- Neurologic Diseases
- Miscellaneous

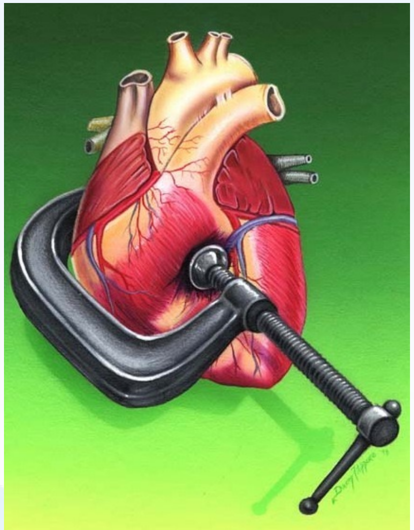
Heart Failure

- Clinical trials have demonstrated that at least three antagonists
  - metoprolol, bisoprolol, and carvedilol—are effective in reducing mortality in selected patients with chronic heart failure.
  - Although administration of these drugs may worsen acute congestive heart failure, cautious long-term use with gradual dose increments in patients who tolerate them may prolong life.
  - Although mechanisms are uncertain, there appear to be beneficial effects on myocardial remodeling and in decreasing the risk of sudden death

Neurologic Diseases

- Propranolol
  - reduces the frequency and intensity of migraine headache.
    - Other β-receptor antagonists with preventive efficacy include metoprolol and probably also atenolol, timolol, and nadolol
  - anxiety ⬇
    - Prophylactically(預防性)
  - stage fright ⬇
  - alcohol withdrawal

- β1 –blocker side effect
  - Heart failure, bradycardia, 血壓低
- β2 –blocker side effect
  - 支氣管痙攣, 末梢血管收縮, 血糖代謝問題

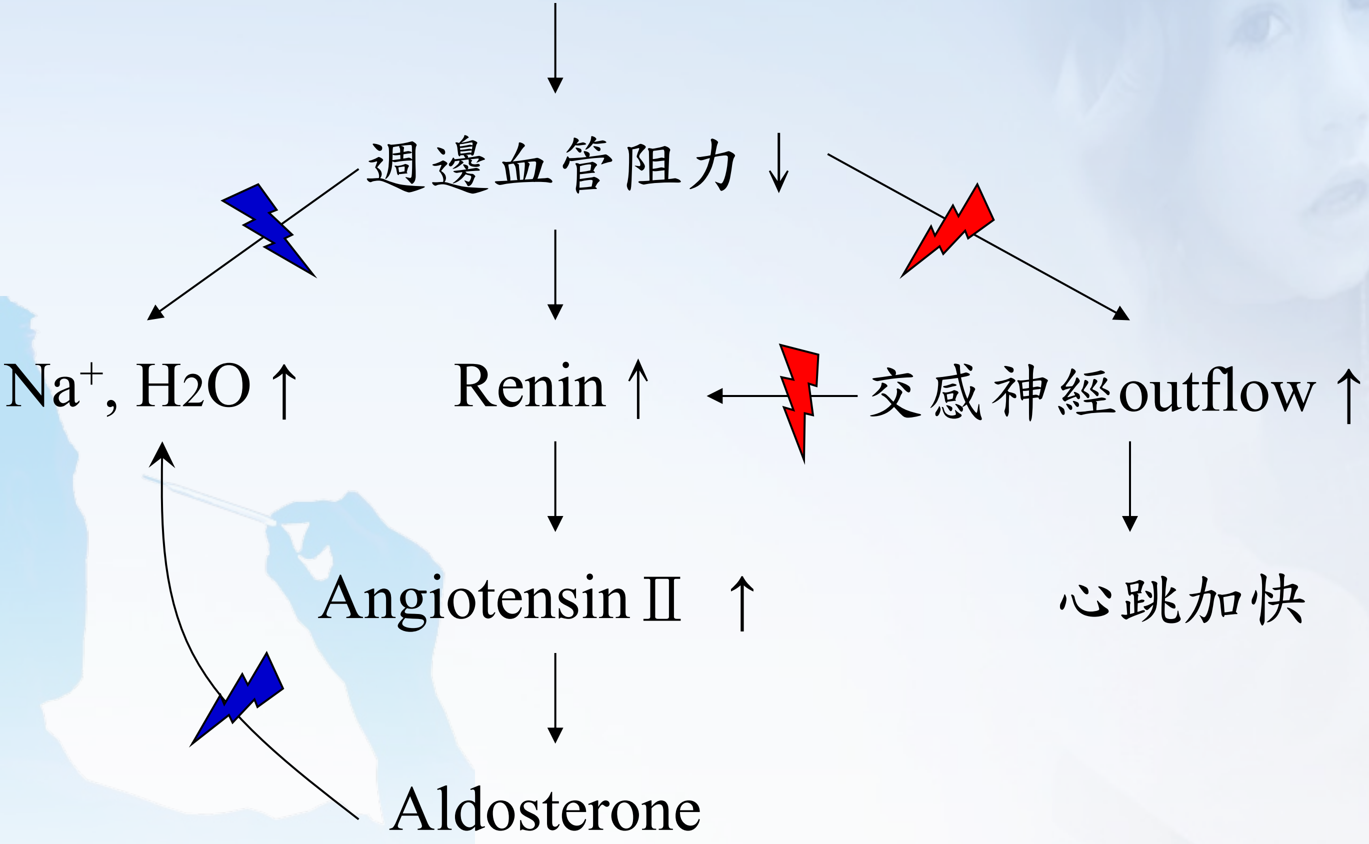


- 選擇性β1–blocker的優點
  – Bronchospasm
  – Peripheral blood flow
  – Peripheral resistance
  – Diabetic patient

併用藥物	交互作用	注意事項
Beta-blockers + Antidiabetic agents (Insulin or Sulfonylureas)	抑制心跳及腎上腺素的作用，遮蓋低血糖症狀，亦可能會抑制胰島素分泌使血糖上生	避免共同服用、或使用具心臟選擇性阻斷劑
Beta-blockers + Phenothiazines,wintermin + Cimetidine + Oral contraceptives	加強beta阻斷效果	降低beta-blockers劑量
Beta-blockers + Barbiturates + Hydralazine + NSAIDs + Rifampin	減弱beta阻斷效果	避免長期併用
Clonidine + Beta-blockers	高血壓反彈(Rebound)	避免一併使用
Clonidine + Tricyclic antidepressant	降壓失效或減弱	避免一併使用

合併療法

- 優點:減少彼此副作用增加降壓效果
- Ex: ***vasodilator*** + ***β-blocker*** + ***diuretics***



Discussion

Chapter 9-Case Study

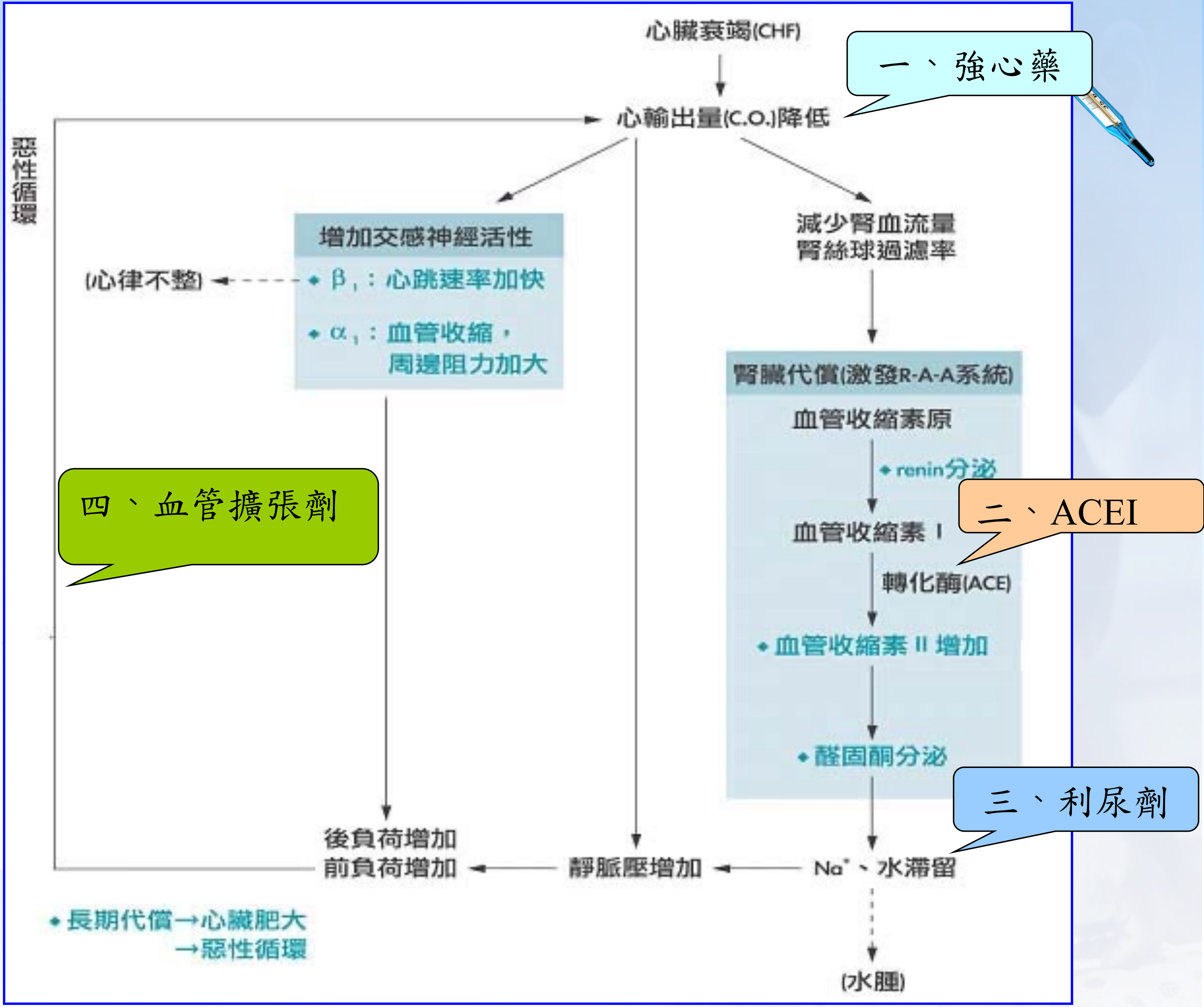
- A 68-year-old man presents with a complaint of light-headedness on standing that is worse after meals and in hot environments. Symptoms started about 4 years ago and have slowly progressed to the point that he is disabled. He has fainted several times, but always recovers consciousness almost as soon as he falls. Review of symptoms reveals slight worsening of constipation, urinary retention out of proportion to prostate size, and decreased sweating. He is otherwise healthy with no history of hypertension, diabetes, or Parkinson's disease. Because of his urinary retention, he was placed on the α_1 antagonist tamsulosin but he could not tolerate it because of worsening of orthostatic hypotension. Physical examination revealed a blood pressure of 167/84 mm Hg supine and 106/55 mm Hg standing. There was an inadequate compensatory increase in heart rate (from 84 to 88 bpm), considering the degree of orthostatic hypotension. Physical examination is otherwise unremarkable with no evidence of peripheral neuropathy or parkinsonian features. Laboratory examinations are negative except for plasma norepinephrine, which is low at 98 pg/mL (normal is 250–400 pg/mL for his age). A diagnosis of pure autonomic failure is made, based on the clinical picture and the absence of drugs that could induce orthostatic hypotension and diseases commonly associated with autonomic neuropathy (eg, diabetes, Parkinson's disease). What precautions should this patient observe in using sympathomimetic drugs? Can such drugs be used in his treatment?

Chapter 10-Case Study

- A 46-year-old woman sees her physician because of palpitations and headaches. She enjoyed good health until 1 year ago when spells of cardiac palpitations began. These became more severe and were eventually accompanied by throbbing headaches and drenching sweats. Physical examination reveals a blood pressure of 150/90 mm Hg and heart rate of 88 bpm. During the physical examination, palpation of the abdomen elicits a sudden and typical episode, with a rise in blood pressure to 210/120 mm Hg, heart rate to 122 bpm, and facial pallor. This is accompanied by severe headache and profuse sweating. What is the likely cause of her episodes? What caused the blood pressure and heart rate to rise so high during the examination? What treatments might help this patient?

Question

Beta blocker 適應證



心臟衰竭(CHF)
心輸出量(C.O.)降低
一、強心藥
惡性循環
增加交感神經活性
(心律不整)
β1：心跳速率加快
α1：血管收縮，
周邊阻力加大
減少腎血流量
腎絲球過濾率
腎臟代償(激發R-A-A系統)
血管收縮素原
renin分泌
血管收縮素 I
二、ACEI
轉化酶(ACE)
血管收縮素 II 增加
醛固酮分泌
三、利尿劑
四、血管擴張劑
後負荷增加
前負荷增加
靜脈壓增加
Na⁺、水滯留
(水腫)
長期代償→心臟肥大
→惡性循環

心絞痛的治療原則

服用Aspirin(100mg)

1. 排除冠狀動脈硬化因子
2. 降低心肌氧氣需求量

a. 減低心跳數:β-blocker
b. 降低前負荷:Nitrates
c. 降低後負荷: β-blocker或Ca^{2+} antagonist
d. 降低代謝需求: β-blocker或Ca^{2+} antagonist

3. 增加心肌氧氣供應量

a. 冠狀動脈擴張: Nitrates或Ca^{2+} antagonist
b. 促進動脈側枝生長
c. 外科手術